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INFLUENCE OF SODIUM BICARBONATE IN PREVENTING RENAL LESIONS FROM MASSIVE DOSES OF SULFATHIAZOLE

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It is well known that the principal lesion which results from the continued administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) or sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) to the experimental animal occurs in the renal tract.[1] Recently two of us (Climenko and Wright[2]) have shown this to be true as regards the monkey (Macacus rhesus) when doses of not more than ten times the therapeutic dose of sulfapyridine or twenty times the usual therapeutic dose of sulfathiazole are administered for long periods. Morphologically, the renal lesions appearing after the administration of sulfathiazole, which differ in a characteristic manner from those following the administration of sulfapyridine, are composed of a series of acute inflammatory reactions around acellular foci, which under in vivo conditions contained crystals of the precipitated drug. In certain of the extirpated kidneys from some of our experimental animals, by the use of a diazotization and coupling technic on rapidly frozen sections, we were able to establish the chemical identity of such crystals as sulfathiazole in the collecting tubules.

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1. Antopol, W., and Robinson, H.: Proc. Soc. Exper. Biol. & Med. **40**:428, 1939. Molitor, H., and Robinson, H.: Arch. internat. de pharmacodyn. et de thérap. **62**:281, 1939. Rake, G.; Van Dyke, H. B., and Corwin, W. C.: Am. J. M. Sc. **200**:353, 1940.

2. Climenko, D. R., and Wright, A. W.: Effects of the Continued Administration of Sulfathiazole and Sulfapyridine in Monkeys, Arch. Path. **32**:794, 1941.

It seemed obvious to us that the major pathologic changes, especially those of the collecting tubules, were the result of physical traumatization of the tissues rather than the result of any specific chemotoxic action of the drug and that such traumatization was due primarily to the precipitation of crystalline material in the renal parenchyma. Therefore, it seemed likely that if such precipitation could be prevented by practical means, the development of the lesions might also be prevented.

Sulfathiazole and acetylsulfathiazole behave as weak organic acids: in general, it is a property of such substances to show increased solubility with increased alkalinity. Thus, below p_H 7.0 the solubility would approach that of sulfathiazole, while with increasing alkalinity the solubility would approach that of the freely soluble sodium salt as its upper limit. This is well known chemical knowledge: Sunderman and Pepper [3] recently indicated the importance of this fact when they stated: ". . . it may be inferred that when crystalline concentrations owing to sulfathiazole therapy threaten, an effort should be made to keep the urine alkaline and to secure a large urinary volume."

The solubility characteristics of sulfathiazole in respect to p_H were demonstrated by the following simple experiment.

A series of buffer solutions ranging from p_H 5.0 to 8.0 in steps of 0.2 were prepared: A phthalate buffer system was used in the range 5.0 to 5.8, while a phosphate system was utilized in the range from 6.0 to 8.0. All p_H values were checked potentiometrically, a glass electrode being used. Aqueous solutions were prepared in duplicate at each p_H value through the addition of a great excess of sulfathiazole or acetylsulfathiazole. The preparations were then kept in an incubator at 37 C. (± 0.5 C.) and agitated continuously for eighteen hours.

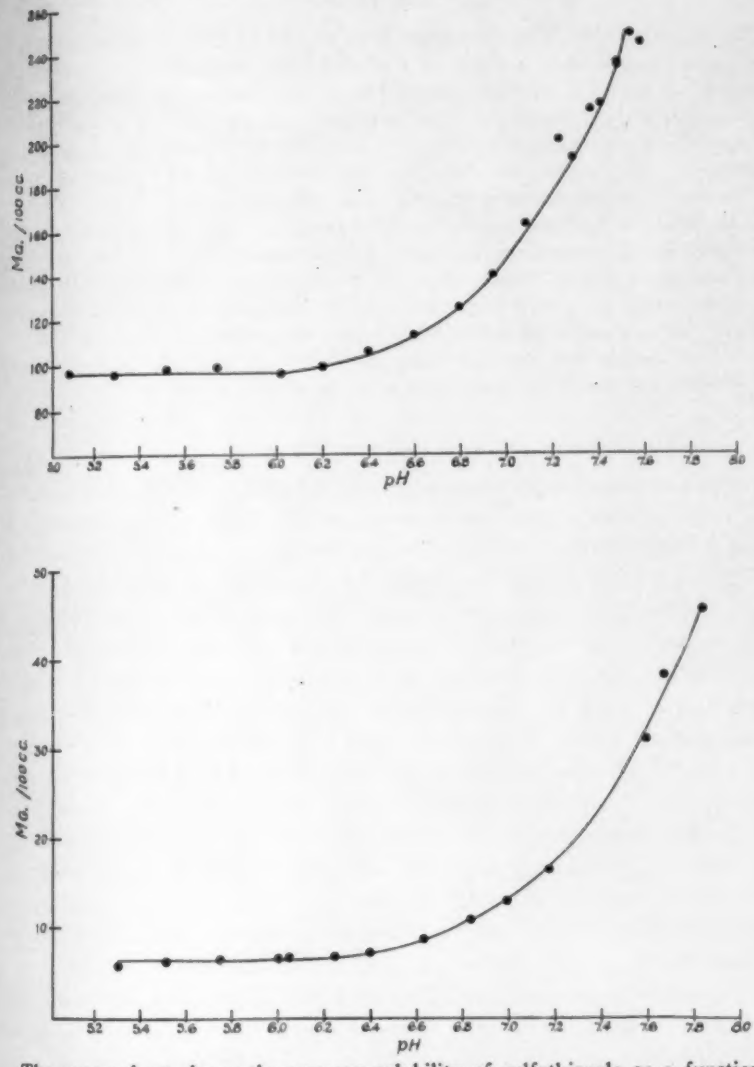
At the end of this time, these mixtures were filtered in the incubator. Aliquot samples of the filtrate were analyzed in duplicate for sulfathiazole or acetylsulfathiazole by a modification of Marshall's methods. The p_H of these filtrates was again checked by means of a glass electrode. It was observed that no significant change occurred in the p_H of the buffer solutions up to a value of 7.2; however the p_H of all solutions above this level was shifted toward the acid side. The shift was considerably greater in the sulfathiazole than in the acetylsulfathiazole series of solutions, a point which would be expected from a consideration of the relative solubilities of the two compounds.

In the establishment of the solubility curves shown in the accompanying charts, the final p_H values, or those present after such shifts occurred, were used.

An examination of these charts will show that the solubility of acetylsulfathiazole is approximately four to five times as great at p_H 7.6 as it is at p_H 6.4 and that the major change in solubility in the physiologic range occurs in the neighborhood of p_H 7.2. The difference in the solubilities of the more soluble free sulfathiazole is numerically much greater

3. Sunderman, F. W., and Pepper, D. C.: Am. J. M. Sc. **200**:790, 1940.

but proportionately less marked. Between p_H 6.4 and 7.4 there is only a twofold difference, with the major change occurring about p_H 7.0. It should be pointed out, however, that the free sulfathiazole is many times more soluble than the acetylated derivative.



The upper chart shows the aqueous solubility of sulfathiazole as a function of the hydrogen ion concentration of the medium at 37 C.; the lower chart, that of acetylsulfathiazole.

In view of this, an attempt was made to duplicate the in vitro findings under in vivo conditions on a series of monkeys with the object of determining whether it would be possible, by suitable therapeutic

measures, to alter the tendency toward precipitation of these compounds in the kidney and thus modify the potential local effects of the compounds on the renal parenchyma.

TECHNIC

The experimental technic duplicated that of our previous work in all details. The animals consisted of a group of 7 normal adult Macacus rhesus monkeys of both sexes. All were kept in individual cages and fed on the usual mixed diet. Medication was by stomach tube and distributed over the day, for it was felt that the continued maintenance of a consistent blood level of the drug was of paramount importance. Accordingly, the daily dose was divided into three equal parts, and the portions were administered at eight hour intervals.

Two monkeys received sulfathiazole in doses of 1.0 Gm. per kilogram per day, while the others received the same dose of sulfathiazole with the addition of an equal amount of sodium bicarbonate. As in our previous work, the sulfathiazole was administered as a milk suspension, and the sodium bicarbonate was given as a 10 per cent aqueous solution immediately after the administration of the drug.

A blood sample was removed four hours after the morning dose was given, for the determination of the concentration of the drug in the blood.

RESULTS

Three animals of a previous experimental group, which were identical with those in this experimental group, were included in the series. At a dose level of 1.0 Gm. per kilogram per day of sulfathiazole, 4 of a group of 5 animals died during the course of medication, which was planned to be continued for twenty-eight days. The pathologic changes observed in the animals of the earlier experimental group have already been described in detail and will not be given here, save to state that they were characterized by multiple acute inflammatory lesions distributed throughout the entire renal parenchyma. In our present series, the kidneys were edematous and moderately congested. On section, there were collections of crystalline material in the larger collecting tubules, but the extreme dilatation of the pelves and ureters described before was not observed. Histologically, the changes resembled those found in monkeys 13 and 14, although in monkey 47 they were not quite so severe. Both animals in this experimental group showed many fibrinous thrombi in the smaller venules.

Of 5 animals on the same dose level of sulfathiazole (1.0 Gm. per kilogram per day) which also received a gram for gram equivalent of sodium bicarbonate, all survived the twenty-eight days of medication without showing any untoward signs other than a moderate degree of diarrhea. Two animals of this group were put to death on the twenty-ninth day for the purpose of necropsy, and no gross pathologic lesions were observed. Sections from these kidneys showed slight acute congestion, most marked in the medullary portions together with a general-

Effects of Continued Administration of Sulfathiazole and Sulfathiazole Plus Sodium Bicarbonate to Monkeys

Medication	Monkey	Blood Concentration (Total, Mg. per 100 Cc.) on Given Day of Medication																	Severity of Renal Lesions
		1	2	3	4	5	6	7	8	10	12	14	16	18	20	22	24	26	28	
Sulfathiazole 1.0 Gm. per Kg. per day	12	....	5.0	1.9	2.4	2.7	8.5	6.5	10.2	8.8	2.8	8.7	10.7	....	10.8	....	10.2	3.6	4.0	Monkey alive and well
	13*	....	14.0	20.8	27.1	45.8	51.4	89.0	87.5	Died	....	....	....	....	....	....	....	....	....	++++
	14*	....	4.5	9.8	50.5	64.5	45.5	Died	....	....	....	....	....	....	....	....	....	....	....	++++
	46*	16.5	18.7	13.0	....	13.2	12.3	14.2	46.8	....	82.6	Died	....	....	....	....	....	....	....	+++
	47*	17.7	15.2	7.1	....	....	11.1	....	8.5	18.7	7.8	....	....	13.7	....	16.0	23.7	39.5	....	Monkey killed; +++
Sulfathiazole 1.0 Gm. per Kg. per day plus $NaHCO_3$ 1.0 Gm. per Kg. per day	48†	18.2	18.9	14.8	....	....	....	....	11.2	15.6	....	23.1	20.1	16.0	20.2	15.2	....	16.3	17.8	Monkey alive and well
	49†	3.6	10.3	13.2	....	....	....	....	14.9	15.6	....	19.2	17.2	11.6	....	17.2	....	25.8	17.1	Monkey killed; +
	50†	6.1	15.6	19.7	....	....	....	....	14.8	21.9	....	22.0	17.1	21.8	....	17.2	....	16.3	17.4	Monkey alive and well
	51†	4.7	11.7	17.3	....	....	....	....	16.8	12.0	....	18.2	....	19.1	....	10.1	....	17.1	25.8	Monkey alive and well
	52†	6.7	12.1	16.0	....	....	....	....	19.2	13.0	....	9.7	14.6	15.6	....	18.8	....	10.5	16.1	Monkey killed; +

* A marked rise of nonprotein nitrogen accompanied the terminal elevation of the blood concentration of the drug.

† The nonprotein nitrogen remained within normal limits throughout the course of the experiment.

ized moderate degree of parenchymatous degeneration of the tubular epithelium. The lumens of the convoluted tubules contained fluid and small accumulations of hyaline bodies, which in no way resembled the crystalline material seen in those animals on the sulfathiazole alone. Foci of acute inflammation were not found. A few collecting tubules contained acidophilic hyaline casts but no crystals. The renal pelves showed no pathologic changes.

As the accompanying table indicates, the clearcut differences between those animals which received sodium bicarbonate in addition to sulfathiazole and those which received sulfathiazole alone cannot be accounted for in terms of differences in blood concentration, for, as we showed in an earlier study,[4] the simultaneous administration of an alkali with sulfathiazole tends to improve the absorption of the drug from the gastrointestinal tract. This point is verified again here.

It must be concluded that the different results obtained in the two groups of animals were dependent on the hydrogen ion concentration of the urine. The nature of the experimental material, however, made it impossible to give these data on a quantitative experimental basis. From previous experimental work, however, we know that such quantities of sodium bicarbonate are capable of maintaining the p_H of the urine of monkeys between 7.2 and 7.4.

Just as an excessive dose of sulfathiazole was used in this experimental series, so the dose of sodium bicarbonate was entirely out of the normal therapeutic range. We would suggest that in clinical practice one should use an amount of a bicarbonate (or another suitable alkali) just sufficient to maintain the urine on the alkaline side of neutrality. As Bridges and Mattice [5] have shown, the amount will vary from patient to patient or even in the same patient from time to time.

CONCLUSIONS

When a dose level of sulfathiazole is used which kills the major portion of experimental animals and produces severe renal lesions in all experimental animals, it is possible to prevent fatalities and also to inhibit the formation of the multiple local inflammatory lesions in the kidney by the administration of large quantities of sodium bicarbonate.

This action of bicarbonate can be accounted for by the fact that both sulfathiazole and its conjugated derivative acetylsulfathiazole are many times more soluble in alkaline mediums than they are in acid mediums and that the maintenance of an alkaline urine prevents precipitation of the drug in the kidney and thereby prevents formation of the local lesions.

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4. Barlow, O. W., and Climenko, D. R.: J. A. M. A. **116**:282, 1941.
5. Bridges, M. A., and Mattice, M. R.: Am. J. M. Sc. **200**:84, 1940.

A CASE OF OSTEOSCLEROSIS WITH EXTENSIVE EXTRAMEDULLARY HEMOPOIESIS AND A LEUKEMIC BLOOD REACTION

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Generalized osteosclerosis is a chronic disease of bone in which there occurs a new growth of bone and connective tissue within the marrow cavity. The cause is obscure except in the cases of certain sclerosing tumors, poisons (e. g., phosphorus or strontium) and perhaps certain inflammatory processes, although the last are usually not generalized. When those cases of the disease in which the cause is obvious are eliminated, the remaining ones may be divided into two main groups: (1) those of Albers-Schönberg's disease and (2) those of osteosclerosis associated with various blood diseases. Albers-Schönberg's disease,[1] *Marmorknochen* or osteopetrosis,[2] is a condition usually discovered during childhood by roentgen examination, since the patients frequently have fractures. There may also be atrophy of the cranial nerves, usually the optic nerves, as a result of narrowing of the foramens of the base of the skull and thickening of the posterior clinoid processes. The cause of this disease is unknown. It is familial, and recently a somewhat similar process has been produced in birds by injecting an estrogen.[3] It seems to be a constitutional disturbance of bone development, involving endosteal and endochondral bone formation, the eburnation depending on a defect of resorption of trabeculae.[1b] Osteosclerosis occurring in conjunction with blood diseases has none of the aforementioned characteristics, being usually a disease of adults, not familial and without atrophy of cranial nerves. Although the two

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1. (*a*) van Creveld, S., and Heybrock, N. I.: Acta pædiat. **27**:462, 1940; abstracted, J. A. M. A. **115**:1756, 1940. (*b*) Schmidt, M. B., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1937, vol. 9, pt. 3, p. 61. (*c*) Alexander, W. G.: Am. J. Roentgenol. **10**:280, 1923.

2. Karshner, R. G.: Am. J. Roentgenol. **16**:405, 1926.

3. Pfeiffer, C. A.; Kirschbaum, A., and Gardner, W. U.: Yale J. Biol. & Med. **13**:279, 1940.

diseases are usually discussed together, it is generally thought now that they represent two entirely different processes.

The findings in the cases of osteosclerosis associated with a blood disease are an enlargement of the spleen, liver and (or) lymph nodes in addition to the osteosclerosis. Some of the patients die as a result of the blood disease, whereas others die of some intercurrent disease (e. g., heart failure, tuberculosis or infections). Many of those patients dying as a result of the blood disease have shown a marked tendency toward bleeding from the mucous membranes and skin and have had a reduced number of platelets in the circulating blood. A few have had marked leukopenia, and in 1 such patient angina was the immediate cause of death. In many of the cases there has been severe anemia.

The liver, spleen and lymph nodes have shown variable degrees of hemopoiesis, which has been the cause of their enlargement. In many of the cases large numbers of megakaryocytes have been described in the areas of blood formation, while in others they have been absent; the latter cases have freqently been those in which bleeding has occurred and in which the platelet counts were low. The blood formation has been described in the sinusoids of the liver, spleen and lymph nodes much as in the case to be presented.

According to the alterations in the cells of the circulating blood and other clinical findings, the cases have been described as osteosclerosis with: (1) myeloid leukemia [4]; (2) myeloid pseudoleukemia, aleukemic leukemia or aleukemia myelosis [5]; (3) anemia [6]; (4) polycythemia,[7] and (5) lymphoid leukemia.[8]

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(Footnotes continued on next page)

In almost all of the described cases immature erythrocytes and granulocytes have been present in the circulating blood. Because of this, there has been some confusion in the diagnosis of these cases; some that were very similar have been designated as instances of different diseases. In the main, however, those cases in which there has been an elevated leukocyte count with immature forms of granulocytes have been called instances of myeloid leukemia, whereas those with a normal total count and only a few or no immature granulocytes have been classified as instances of myeloid pseudoleukemia or of anemia. The distinction between the cases of pseudoleukemia and the cases of anemia is not very sharp.

The external appearance of the bones has been normal in all except 3 of the described cases of osteosclerosis. In 2 of the exceptions there was periosteal thickening, and the condition occurred in children [5h, n]; one had osteophytes of the ribs and skull. On section of the long bones there is seen to be a marked increase in density of the cancellous bone of the epiphyses and of the ends of the diaphyses. In addition to this, the cancellous bone extends toward the center of the diaphyses, so that much of the diaphysial marrow cavity may be replaced by spongy bone. The cortex of the bone has usually been described as thickened, in some cases as much as 8 mm. more than normal,[9] the newly formed bone having been laid down on the inner surface of the cortex, beneath the endosteum. In a few cases the cortex has been normal in thickness.[5e, n] The increase of spongy bone and the thickening of the cortex of the diaphyses may so greatly restrict the marrow space of the long bones that the only remaining marrow may be a small thin zone in the middle third of the bone. The flat bones have marked increase of density, with so little marrow space remaining that frequently no marrow can be expressed from the cut surface. The color of the marrow has been described as yellow, gray or red, these variations apparently being due to the relative amounts

J. Path. & Bact. **45**:383, 1937. (*q*) Hickling, R. A.: Quart. J. Med. **6**:253, 1937. (*r*) Carpenter, G., and Flory, C. M.: Arch. Int. Med. **67**:489, 1941.

6. (*a*) Donhauser, J. L.: J. Exper. Med. **10**:559, 1908. (*b*) Chapman, E. M.: Am. J. M. Sc. **185**:171, 1933. (*c*) Conrad, H. E.: Deutsche med. Wchnschr. **64**: 1404, 1938. (*d*) Schmidt, M. B.: Beitr. z. path. Anat. u. z. allg. Path. **77**:158, 1927. (*e*) Zadek, I.: Klin. Wchnschr. **7**:1848, 1928. (*f*) Vaughan, J. M.: J. Path. & Bact. **42**:541, 1936. (*g*) Vaughan, J. M., and Harrison, C. V.: J. Path. & Bact. **48**:339, 1939. (*h*) Schmidt [1b] (*i*) Assmann.[5a]

7. (*a*) Hirsch. E. F.: Arch. Path. **19**:91, 1935. (*b*) Rosenthal, N., and Bassen, F.: Arch. Int. Med. **62**:903, 1938. (*c*) Stone, E. M., and Woodman, D.: J. Path. & Bact. **47**:327, 1938.

8. Zypkin, S. M.: Folia haemat. **35**:7, 1928.

9. Schwarz.[4g] Assmann.[5a] Nauwerck and Moritz.[5b] Oesterlin.[5h]

of remaining hemopoietic or fat tissues present. There has been considerable variation in the extent of the sclerosis in different cases.

The principle microscopic bone changes are an increase in the number of bony trabeculae and a replacement of the marrow spaces with a loose, fairly cellular connective tissue. In cancellous bone the increase in trabeculae may be so great that in a field which would normally contain only two or three spicules there may be ten or twelve. The newly formed trabeculae are fairly narrow and short and contain a central calcified zone, surrounded by a dense connective tissue; they communicate with each other to form a dense network of bone. A well defined layer of endosteum is difficult to see. The cells within the trabeculae are large and irregular, and there is an absence of definite lamellar striation. The remaining marrow spaces are filled with a connective tissue containing a number of nuclei and are traversed by rather large veins and arteries; the normal network of sinusoids and reticulum is absent. The marrow from the diaphyses consists of a fatty tissue, which may show extensive gelatinous changes, or the marrow may be replaced by a cancellous tissue similar to that already described. In most of the reported cases only a few small islands of hemopoietic tissue persist; these are intravascular or surround the veins. In a few cases the remaining marrow space of the middle third of the diaphysis has shown active hemopoiesis. The histogenesis of the bone lesions is not entirely clear, since in most of the cases the lesions have been completely inactive at the time of autopsy.

DESCRIPTION OF CASE

The features of special interest in the case here investigated include: (1) practically complete absence of hemopoietic tissue in the bone marrow in conjunction with a substantially normal red cell count; (2) hyperplasia of bone in relation to fibrosis of the marrow; (3) extensive extramedullary blood formation; (4) a "division of labor" as regards hemopoiesis in that erythrocytes were formed almost exclusively in the lymph nodes and the liver, and granulocytes, in the spleen; (5) evidence that lymphocytes served as common ancestors for both erythrocytes and granulocytes; (6) evidence that the macrophages with erythrocyte fragments in the sinuses of the lymph nodes arose from cells of the reticular stroma.

The pertinent clinical history can be briefly summarized:

A 55 year old white farmer entered the University of Virginia Hospital one month before his death. His illness began two years before death, with dyspnea, weakness, orthopnea and palpitation. At this time his physician told him that he had an abdominal mass (spleen?). Four months before death the aforementioned symptoms became more severe, edema of the extremities and ascites developed, and it was necessary that he cease working.

He was poorly nourished and dyspneic. The cervical and axillary lymph nodes were palpable but small. The blood pressure was 100 systolic and 80 diastolic. The liver could be palpated 7 to 8 cm. below the costal margin; the spleen extended to the iliac crest. There were ascites and a pitting edema of the legs, hands and genitalia. The gastric juices contained free hydrochloric acid. The icterus index was 4.4. The blood counts are given in the table.

The symptoms of heart failure became more severe, and clinically his death was a result of heart failure.

The necropsy report includes the following directly pertinent data: The weight of the liver was 2,010 Gm.; that of the spleen, 1,390 Gm. The lymph nodes were moderately enlarged. The bone marrow was friable, gray and without fat. The parathyroids were normal in number, size, distribution and histologic pattern.

The diaphysis of the femur contained numerous spicules of bone (fig. 1). The marrow spaces were filled with a fibrogelatinous connective tissue. There was practically no hemopoietic parenchyma. The blood vessels were relatively few. Some long, straight, open capillaries and open veins occurred, but others were collapsed,

Blood Pictures *

Date	Hemoglobin Content, %	Red Blood Cells, Millions	White Blood Cells	Lymphocytes	Monocytes	Premyelocytes	Myelocytes	Juvenile Forms	Bands	Segmented Forms	Eosinophils	Basophils
3/16	40	3.2	22,600	9	0	8	19	13	20	27	0	4
3/17	60	3.5	26,800	20.5	0.5	7.5	18.5	10	7.5	34	0	1.5
3/22	58	4.0	24,000	33	0	15	10	1	6	33	0	2
4/8	52	4.0	32,000	10	0	25	15	5	10	29	0	6
4/12	55	4.1	25,000	22	0	6	20	4	12	32	1	3

* The red cells were characterized by anisocytosis, poikilocytosis and polychromatophilia; a few normoblasts were seen on all examinations; the platelets were normal in number and structure; the blood smears showed no megakaryocytes.

and some of the veins showed regions bare of endothelium and had local defects in their walls. There were a few more or less degenerate megakaryocytes, generally in the venous sinuses.

Sections of the vertebrae showed considerable osseous hyperplasia (fig. 2). However, the osteoblasts had a degenerate appearance and at the time of death were probably no longer active. The marrow spaces were filled with a fibrous connective tissue, including a few magakaryocytes and an occasional osteoclast. Very numerous megakaryocytes occurred in the venous sinuses. Hemopoietic parenchyma was extremely sparse. Blood vessels were numerous and open. Some of the venous sinuses contained blood. This almost completely aplastic marrow still had an apparently efficient circulation. It may be assumed that the marrow of the ribs and sternum was similarly fibrotic and without hemopoietic significance.[10]

A striking feature of the lungs was the relatively large number of more or less degenerate megakaryocytes in the alveolar capillaries. Even normal lungs contained a variable small number of intracapillary megakaryocytes, practically naked giant cell nuclei and giant platelets. These cells, nuclei and plastids entered the venous sinuses of the bone marrow and were transported to the right side

10. Gordon, A. S.: J. Lab. & Clin. Med. **24**:352, 1939.

of the heart with the blood from the superior and inferior venae cavae, and thence to the lungs, where they were filtered out in the alveolar capillaries.[11]

In the marrow spaces of the femurs and vertebrae the walls of the venous sinuses showed numerous breaks, thus allowing admission to the venous drainage of an unusual number of megakaryocytes, which subsequently became lodged in the capillaries of the pulmonary alveoli. Megakaryocytes were especially numerous in the venous sinuses of the marrow spaces in the vertebrae. To this accession from the morbid aplastic bone marrow were added even larger contributions from

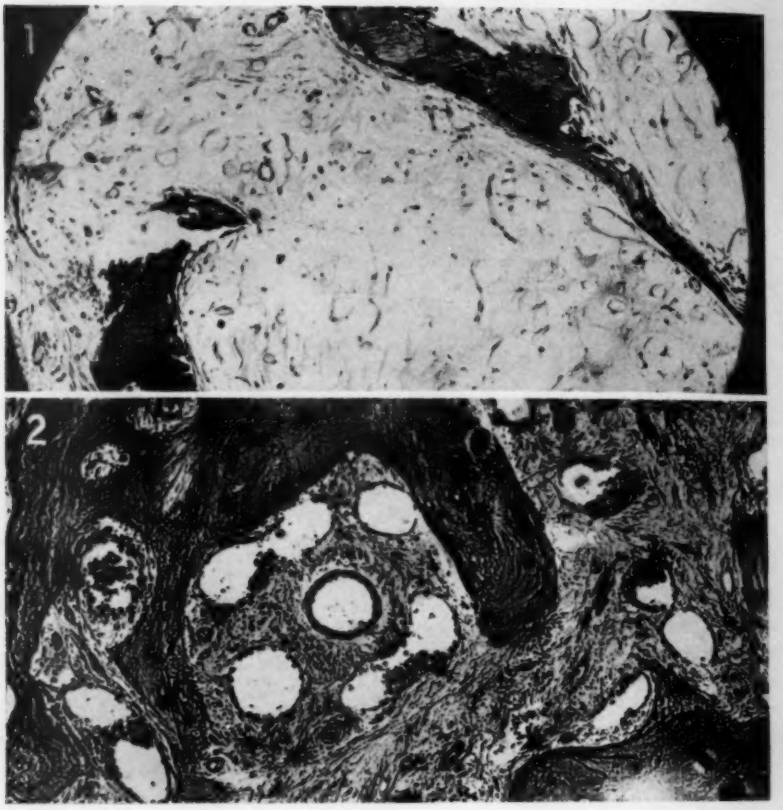

Fig. 1.—Area of the diaphysial marrow of a femur, showing two osseous spicules. The marrow consists of fibromucous connective tissue with only meager traces of degenerating hemopoietic tissue. × 77.

Fig. 2.—Area of vertebral marrow, showing extensive osseous hyperplasia. The marrow consists of a relatively vascular fibrous connective tissue with very meager hemopoietic tissue. Note, near the center, an empty arteriole almost completely enveloped by four venous sinuses. × 92.

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11. Jordan, H. E.: Anat. Rec. **77**:91, 1940.

the lymph nodes and the liver. All of these circulating megakaryocytes ultimately became lodged in the lung capillaries.

Sections of the greatly enlarged spleen showed a fairly compact cellular composition with considerable fibrosis and practically no mitotic activity. Granulocytopoiesis was relatively very active. There was discernible only meager erythrocytopoietic activity in the venous sinuses. There occurred only a few degenerate small megakaryocytes, mostly as naked tachychromatic nuclei. The progressive fibrosis produced compression and collapse of many of the venous sinuses, a condition unfavorable for erythrocyte maturation. Compared with conditions in certain lymph nodes and the liver, only a relatively small number of normoblasts was discernible in the spleen.

In the liver erythrocytopoiesis was active. The capilliform sinusoids were in many places well filled with cells representing all stages in the maturation of erythrocytes: hemocytoblasts, proerythroblasts, erythroblasts, normoblasts and red corpuscles. This condition was especially pronounced near the axis of the hepatic lobule. The intracapillary cell groups included also numerous megakarocytes, active in platelet production. There was no evidence of a hemocytogenic significance of the lining cells of the hepatic capillaries. A few of the sinusoids were filled almost exclusively with small lymphocytes.

The megakaryocytes as a group comprised a practically complete series of progressive and regressive stages. Many of the older megakaryocytes were polynucleated, in contrast with the more general condition in which the nucleus was of the characteristic basket form. There was no evidence of granulocyte production in the liver. The conclusion indicated that the hepatic megakaryocytes developed in situ; a complete developmental series could be traced from ancesteral hemocytoblasts to the definitive giant cells, and these cells were obviously too large to have been carried intact through the capillary rete of the alveoli of the lungs.

The lymph nodes available for microscopic study included specimens from the right and left axillary regions and the right and left inguinal regions, as well as several peritracheal, periaortic, abdominal and mesenteric nodes. A left inguinal and a right axillary node were almost completely fibrotic. A peritracheal node consisted of fibrous connective tissue and scattered areas of more or less compact lymphoid tissue in about equal proportions. Two left axillary nodes showed fibrous areas in the proportion of approximately one volume to two of nodular and cordal lymphoid tissue. In both nodes many of the sinuses were almost completely filled with stellate reticular cells. The meshes enclosed a relatively small number of megakaryocytes and erythroblasts. Some of the reticular cells had differentiated into macrophages and contained a variable amount of erythrocyte fragments.

A periaortic abdominal and a right inguinal node had very wide sinuses well filled with numerous megakaryocytes in all stages of progressive and regressive changes, some with pseudopods in process of segmentation into platelets, and cells in all stages of differentiation from the initial hemocytoblast to the normoblast and definitive erythroplastid—in all essential respects, like conditions in the hepatic capilliform sinusoids (figs. 3, 4 and 5). The ancestral cells were large and medium-sized lymphocytes, serving as hemocytoblasts. The endothelioid cells lining the sinuses showed no mitoses and were independent of the erythrocytopoietic process. Megakaryocytes appeared both in the more compact lymphoid parenchyma and in the sinuses. Those in the parenchyma were, in general, younger stages, and a few of these were seen in various phases of mitosis. Transitional stages between these younger megakaryocytes and large lymphocytes were also present

in the parenchyma. The megakaryocytes of these lymph nodes obviously began differentiation in the parenchyma and became transferred at various stages of development to the sinuses. The more compact parenchyma contained also many small plasma cells, a moderate number of immature granulocytes and a few mast cells. Several lymph nodes had sinuses well filled with blood and resembled hemal nodes.

Macrophages of reticuar cell origin, with erythrocyte debris, occurred in considerable number only in the lymph nodes which showed considerable fibrosis. The

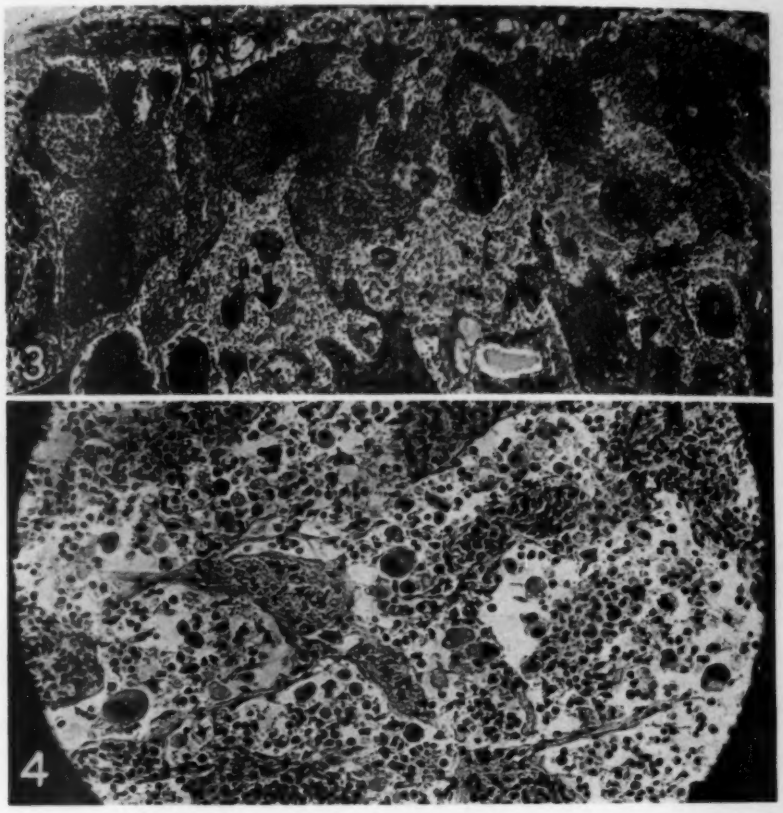

Fig. 3.—Section of a periaortic abdominal lymph node, including portions of the capsule (above), cortex and medulla. Note the decrease in size and alteration in form of the cortical nodules and medullary cords and the reciprocal enlargement of the sinuses. The sinuses are well filled with cells, including megakaryocytes, hemocytoblasts, erythroblasts, normoblasts and macrophages with erythrocytic debris. × 15.

Fig. 4.—Arrow-indicated area of figure 3 at higher magnification. Numerous megakaryocytes are conspicuous. × 418.

progressive fibrosis in these nodes presumably produced a disjunction of the intranodal sinuses from the afferent and efferent lymphatics. Erythrocytes apparently developed from the entrapped lymphocytes, and the presence of red corpuscles

and their disintegration products in the stagnant lymph of these blind sinuses stimulated the production of macrophages.

In the nonfibrotic nodes with the wide sinuses filled with erythropoietic tissue, including numerous megakaryocytes, the efferent lymph drainage was presumably still open, and the megakaryocytes and maturing erythrocytes found their way to the superior vena cava via the thoracic duct and the right lymphatic duct. The megakaryocytes after free passage through the right side of the heart were filtered

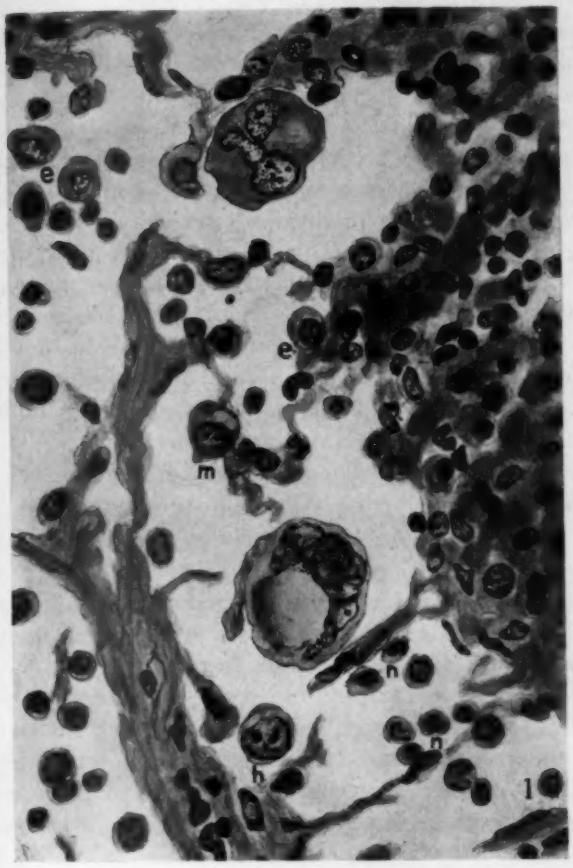

Fig. 5.—Drawing of a portion of a medullary sinus of a right inguinal lymph node. At the right of the figure is a portion of a medullary cord; near the left, a coarse trabecula. The sinus contains two megakaryocytes. Approximately midway between these two giant cells are a macrophage (*m*) and an erythroblast (*e*). At the upper left hand border is a group of three erythroblasts (*e*). Below the lower megakaryocyte occurs a hemocytoblast (*h*), several normoblasts (*n*) and a typical small lymphocyte (*l*). The sinal area at the lower left hand corner contains a group of small and medium-sized lymphocytes. × 800.

out in the capillaries of the pulmonary alveoli. This accession from lymph node sources accounted in part for the excessive number of giant cells in the lungs.

COMMENT

The histologic evidence from the study of lymph nodes, marrow, spleen, lungs and liver, together with the fact that the red cell count was essentially normal, suggests the following interpretation. There was operative some unknown primary factor favoring widespread fibrosis. This factor expressed itself first in the bones, where it produced extensive osseous hyperplasia with concomitant fibrosis of the medullary stroma and disappearance of hemopoietic parenchyma. Compensation for the disappearance of hemopoietic tissue from the bone marrow was made by the potentially hemopoietic tissues: spleen, liver and lymph nodes.

Study of microscopic sections of these organs revealed that all three were actually active in blood formation—lymph nodes and liver predominantly in red cell production, the spleen predominantly in granulocyte production. The explanation for this "division of labor" in blood cell production remains uncertain. However, the lymph nodes are generally the first tissues to respond in compensation for hemopoietic dysfunction of the marrow.[12] But in this case the primary factor of fibrosis early affected also the compensatory lymph nodes. At death many of the lymph nodes were completely fibrotic; some remained in a condition of active erythroid metaplasia. A period must have come in this progressive fibrosis of the lymph nodes when this tissue could no longer adequately supply the red cell demands. At this point presumably it was the spleen that undertook the work of furnishing ancestral cells for hemopoiesis.

The spleen became actively hyperplastic and enlarged to more than five times the normal size. But conditions in the spleen were favorable only for granulocyte maturation. We may suppose that the extensive hyperplasia and concomitant fibrosis compressed the venous sinuses, generally favorable for compensatory extramedullary red cell maturation, to such a degree that conditions were no longer suitable for erythrocytopoiesis. The enormously excessive number of lymphocytes produced by the spleen during the period of its great enlargement entered the circulation and were filtered out in the hepatic capillaries, where they served as ancestors for the production of erythrocytes. These hepatic capilliform sinusoids, areas of slowly moving blood with a relatively high carbon dioxide tension, were apparently similar in essential erythrocytopoietic factors to those of bone marrow and could accordingly provide compensatory area for red cell production. Red cell production was almost exclusively a process of transformation of lymphocytes; mitosis was practically absent among the cells of the hepatic sinusoids.

12. Jordan, H. E.: Arch. Path. **18**:1, 1934; **23**:653, 1937; **27**:1, 1939.

The fundamentally important fact which emerged from this study concerns the pluripotential hemopoietic function of the lymphocytes. The problem of the function of the lymphocytes has long been one of the most important in medical science. The data from this study give further support to the interpretation of the lymphocyte as an embryonal cell with multiple developmental potentialities, including most prominently that of serving as a common ancestor (hemocytoblast) for the several varieties of blood cells: erythrocytes, granulocytes, monocytes, plasma cells and megakaryocytes.[13] In the extramedullary sites of blood formation, lymph nodes, spleen and liver, the small lymphocytes grew to the size of large lymphocytes, meanwhile acquiring the cytologic features of hemocytoblasts. Such hemocytoblasts differentiated into erythrocytes within the sinusoidal channels with relatively stagnant blood high in carbon dioxide content (venous sinuses of marrow, capilliform sinusoids of liver, sinuses of modified lymph nodes) and into granulocytes in the intervascular parenchymal areas.

In these lymph nodes, as in bone marrow under normal conditions, the erythrocytes developed in the endothelium-lined channels, lymphatic and venous, respectively; and granulocytes developed only in the intervascular parenchyma. Presumably areas of relative lymph stasis contain similarly favorable stimuli, especially relatively high carbon dixoide tension, for the maturation of erythrocytes. Lymph nodes and bone marrow have practically identical ancestral cells, large lymphocytes and hemocytoblasts, respectively.

Both in the lymph nodes and in normal bone marrow the cells of the intervascular parenchyma include variable numbers of plasma cells. These plasma cells pass through developmental stages in all respects apparently similar to the maturation phases of erythrocytes with the exception of an absence of hemoglobin content. They may divide by mitosis; the nucleus contracts and becomes progressively more chromatic; the nucleus may disappear by intracellular resorption or by extrusion, sometimes in relation to a preceding fragmentation, and the final product is an ahemoglobiniferous plastid comparable in size with an erythroplastid. Occasional plasma cells are binucleate, practically identical with the occasional binucleate proerythroblasts of normal erythropoietic bone marrow.

The extensive removal of erythrocytes by macrophages of reticular cell origin in the sinuses of some of the lymph nodes calls for special consideration. The erythrocytes of the sinuses developed from local lymphocytes. Such an origin could be clearly traced through a series of transitional stages within the sinuses. Some of these sinuses had presumably become disconnected from the lymphatic system. Condi-

13. Jordan, H. E.: Am. J. Anat. **59**:249, 1936.

tions thus became especially favorable for the transformation of entrapped lymphocytes into erythrocytes. Their presence in the blind sinuses stimulated the production of macrophages, which functioned as scavengers for the removal of the degenerating erythrocytes and their debris. In the case of sinuses still in connection with efferent lymphatics the maturing erythrocytes had ready access to the blood vessel system. In the earlier stages of lymph node transformation (erythroid metaplasia) conditions in the sinuses, with slowly moving lymph, were likewise presumably such as favored lymphocyte differentiation into erythrocytes and in these cases the red corpuscles could gain access to the blood via the thoracic duct and the right lymphatic duct.

The alternative interpretations of the ancestral cells of the erythroblasts of extramedullary foci of blood formation in postfetal stages are: (1) hemocytoblasts transplanted from the bone marrow ("colonization theory"); (2) stromal reticulum cells ("local formation theory"); (3) large lymphocytes. Each of these interpretations has had the support of competent hematologists. The data from this case of osteosclerosis favor the claim that lymphocytes furnish the ancestral cells for the production of erythrocytes in areas of erythroid metaplasia. The evidence from the microscopic study of the lymph nodes and the liver in this case is twofold: (1) a direct series of transitional stages from small lymphocyte, through large lymphocyte, proerythroblast ("megaloblast"), erythroblast, normoblast, to erythroplastid; (2) practical absence of erythropoietic tissue in the bone marrow. Furthermore, the coincidence of an enormous enlargement of the spleen and the presence of enormous numbers of lymphocytes, hemocytoblasts and maturing nonproliferating erythrocytes in the capilliform sinusoids of the liver favors the interpretation of a filtering out of splenic lymphocytes in the hepatic capillaries, where they served as precursors of the red cells.

COMMENT

The occurrence of certain blood diseases in association with a bone lesion that has completely or almost completely replaced the normal adult organ of hemopoiesis has been an observation that has interested every one who has studied such a case, and almost every one of the investigators has offered some explanation of this relationship. With few exceptions, in all of the cases studied the blood disease has been recognized during life, but the bone disease has not been discovered until autopsy. This, of course, is easily explained by the fact that the patients have no symptoms referable to the bones, as in the case of Albers-Schönberg's disease, and roentgen studies are not carried out during life. It is worthy of note here that during the last decade there have been a number of roentgen studies of bones in series of

cases of leukemias, and in none of these has osteosclerosis been described.[14] Since the osteosclerosis has usually not been discovered until the disease has progressed quite far, any comment on the casual relationship of the two processes is largely speculative. The speculations may be divided into four main groups: (1) that the association is purely accidental, (2) that the osteosclerosis is a result of the blood disease, (3) that the various blood diseases are a result of the osteosclerosis and (4) that the two processes occur together at the same time, being brought about by the same etiologic factor.

Heuck,[4a] who described the first case of leukemia associated with osteosclerosis, thought that the bone lesions were accidental findings. This idea, however, has not since been generally accepted. Neumann,[15] in discussing Heuck's case, put forth the idea that the osteosclerosis represented a late or end stage of an originally hyperplastic or leukemic bone marrow; this conception has been presented in somewhat altered forms by a number of writers on the subject.[16] Jores [5e] expressed the opinion that the medullary fibrosis is a reaction of the marrow in an attempt to limit the disease. Others have proposed the idea that the two processes are a result of the same etiologic action, that a toxin is responsible [6a] for the osteosclerosis and that under such circumstances the toxin which causes the leukemia may lead to fibrosis, much the same as in Hodgkin's disease.[8] Schmidt [6d] expressed the belief that the two processes are coordinated through an interaction of the bone marrow disease and the endosteum.

Recently [17] the idea has been expressed that the osteosclerosis is the primary disease and that the extramedullary hemopoiesis, being vicarious and not normal during adult life, may result in abnormal blood pictures. With this conception the cases with anemia or leukopenia could be thought of as cases in which the liver, spleen and (or) lymph nodes have been unable to supply the necessary cells, whereas those with leukemia or polycythemia could be thought of as cases in which these organs in their zeal to supply blood have overshot the mark. It has been suggested that extramedullary hemopoiesis may not be restrained by the same factors as normal medullary hemopoiesis. By the same reasoning the occurrence of immature and abnormal forms of erythrocytes or granulocytes in the circulating blood can be explained.

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14. Clark, J. J.: Radiology **26**:237, 1936. Connor, C. L.: Am. J. Cancer **29**: 20, 1937. Doub, H. P., and Hartman, F. W.: J. A. M. A. **105**:942, 1935. Erb, I. H.: Arch. Dis. Childhood **9**:319, 1934.

15. Neumann, E.: Klin. Wchnschr. **17**:281, 1880.

16. Schmorl.[4b] Lehndorff and Zak.[4c] von Baümgarten.[4e] Assmann.[5a] Reiche.[5g] Hirsch.[7a]

17. Reiche.[5g] Oesterlin.[5h] Mettier and Rusk.[5j] Donhauser.[6a]

With this conception the disease would not be considered true leukemia or polycythemia, but the findings on which a diagnosis of leukemia is based (myeloid metaplasia of the lymph nodes, liver and spleen and the presence of immature cells in the circulating blood) are directly the result of the extramedullary hemopoiesis. In support of this idea may be offered the occurrence of all the findings necessary for the diagnosis of leukemia or aleukemic leukemia in some cases of sclerosing bone tumors.[18] In these cases there is usually anemia, with enlargement of the spleen, liver and lymph nodes, and immature cells may occur in the circulating blood, with a reduced, normal or elevated white cell count (leukoerythroblastic anemia [6f]). Whether or not any of these cases could be looked on as cases of true leukemia is doubtful; however, in Weber's [15a] case the total white cell count reached 51,000 of which 37 per cent were myelocytes.

The diagnosis of pseudoleukemia, aleukemic myelosis or aleukemic leukemia in these cases of osteosclerosis may also be doubted. The diagnosis has been made on the presence of the enlargement of the spleen, liver and lymph nodes, which have shown myeloid metaplasia. However, this metaplasia may have been compensatory, the result of a decrease or absence of available marrow space for normal hemopoiesis, and was probably on a basis entirely different from that of true leukemia or aleukemic leukemia, in which there is myeloid hyperplasia of the bone marrow. This possibility led Mavros [51] and others to call the process *nicht leukaemische* myelosis. Since in most of the cases reported as instances of aleukemic leukemia with osteosclerosis there were immature granulocytes in the circulating blood in addition to enlargement of the spleen and liver, it is doubtful whether this nomenclature is correct, because true aleukemic leukemia should have no immature granulocytes in the circulating blood.[19] In fact, many of the conditions described as osteosclerotic anemia have also been characterized by the presence of immature granulocytes and probably should have been called leukemia, if the blood picture during life is used as a basis for the diagnosis. Recently a few cases [20] have been described in which there was marked hyperplasia of bone marrow in conjunction with extramedullary hemopoiesis and in which the quantity of hyperplastic marrow was greater than normal. The osteosclerosis and

18. (*a*) Weber, F. P.: Tr. M. Soc. London **52**:99, 1929; (*b*) J. Path. & Bact. **32**:171, 1929. (*c*) Askanazy, M., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1927, vol. 1, pt. 2, p. 902. (*d*) Rush, G. Y., and Miles, W. L.: Am. J. Path. **3**:289, 1927. (*e*) Mavros.[51]

19. Jaffé, R. H.: Arch. Path. **3**:56, 1927.

20. Vaughan and Harrison.[6g] Stone and Woodman.[7c]

the hyperplasia of marrow cells in these cases have been interpreted as a result of some unknown stimulation affecting both types of cells.

SUMMARY

A case of generalized osteosclerosis has been studied which clinically was thought to be one of chronic myeloid leukemia. Evidence has been presented which led us to believe that this case was not one of true myeloid leukemia but so far as the leukemoid features were concerned a case of extensive extramedullary hemopoiesis. Studies of the sites of extramedullary hemopoiesis—the spleen, liver and lymph nodes—have shown that the various blood elements are derived from common ancestral cells, the lymphocytes. Erythrocytopoiesis occurred chiefly in the liver and lymph nodes, and granulocytopoiesis, in the spleen.

DEVELOPMENT OF NEWBORN RAT OVARIES IMPLANTED IN THE ANTERIOR CHAMBERS OF ADULT RATS' EYES

ADULT RATS USED: NORMAL, GONADECTOMIZED, AND GONADECTOMIZED TREATED WITH CHORIONIC GONADOTROPIN

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Inasmuch as some of us have been interested in various phases of ovarian reactions and neoplasms, we undertook an investigation of the development of immature ovarian rat tissue transplanted into the anterior chambers of adult rats' eyes as influenced by various endogenous hormonal stimuli and exogenous chorionic gonadotropin. It was felt that any departure from the normal development might throw some light on the genesis of ovarian tumors.

The reactions of ovarian tissues to various hormonal influences make the ovary a favorable organ for study, especially because it can be transplanted into the anterior chamber of the eye. Here it can be observed from day to day as various influences affect it in its altered environment. The anterior chamber of the eye is a favorable site for transplantation of tissue because of the nutritional conditions and the absence of invasion of the transplant by tissues of the host. In 1873 van Dooremal[1] used the anterior chambers of the eyes of dogs and rabbits for implantation of tissue and foreign bodies and suggested these chambers as sites for studying neoplasms. Schochet[2] in 1920 transplanted rat ovaries into the anterior chambers of rats' eyes in order to observe ovarian function.

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1. van Dooremal, J. C.: Arch. f. Ophth. **19**:359, 1873.
2. Schochet, S. S.: Surg., Gynec. & Obst. **31**:148, 1920.

The work of many investigators shows that the development of ovarian transplants depends not only on the stage of development of the ovarian tissue but also on the endocrinal state of the host. Evidence has accumulated that homotransplants of immature tissues are more often successful than those of adult tissues and grow more rapidly. As early as 1901 Foà [3] observed the acceleration of growth of the newborn rabbit's ovary transplanted intra-abdominally into the adult rabbit. The effect of the host on the development of the transplant has been shown by Goodman [4] in experiments in which immature rat ovaries were transplanted to anterior chambers of eyes; he observed a relatively low percentage of "takes" in normal females, a higher percentage in normal males castrated two months after implantation and a still higher percentage in spayed females. May [5] observed slow growth of 3 day old rat ovaries transplanted to the anterior chambers of the eyes of young rats. These different influences of the host also manifest themselves in the histologic development of these anterior chamber transplants, as shown by the follicular development found in male rats by Goodman [4] and by Pfeiffer [6] and by the corpus luteum formation observed in spayed females by Goodman [4] and by May.[5] These changes correspond to those found in similar ovarian transplants at other sites.

Anterior chamber ovarian transplants not only develop in a definite manner but possess functional activity. This is shown by the appearance of estrous cycles in spayed rats bearing these grafts. Goodman [4] observed the estrous cycles of spayed hosts, and May [5] found that the cycles appeared between thirteen and twenty-seven days after transplantation of 3 day old rat ovaries.

Anterior chamber ovarian transplants are capable of responding to hormonal stimulation. Dworzak and Podleschka [7] and others have suggested their use in a test for pregnancy, and Goodman [4] tested the viability of the grafts by treatment of the host with chorionic gonadotropin (antuitrin S).

It has been suggested that tissue transplanted to a foreign environment might give rise to tumor formation. In 1881 Leopold [8] transplanted rabbit fetal cartilage to the anterior chambers of the eyes of rabbits. He expressed the belief that the fetal cartilage, which increased two hundred to three hundred times in mass, formed true chondromas,

3. Foà, C.: Arch. ital. di biol. **35**:364, 1901.
4. Goodman, L.: Anat. Rec. **59**:223, 1934.
5. May, R. M.: Bull. d'histol. appliq. à la physiol. **17**:51, 1940.
6. Pfeiffer, C. A.: Anat. Rec. **65**:213, 1936.
7. Dworzak, H., and Podleschka, K.: Zentralbl. f. Gynäk. **60**:1928, 1936.
8. Leopold, G.: Virchows Arch. f. path. Anat. **85**:283, 1881.

whereas adult cartilage transplants were resorbed. Later Zahn [9] found no evidence of neoplastic change in similar cartilage transplants, and von Tiesenhausen [10] failed to find true tumor formation in undifferentiated embryonal transplants in hens' eyes. The observations of previous workers suggest the possibility that mucous membrane transferred to an abnormal environment has a tendency to form cysts. In 1874 Goldzieher [11] described a cystic structure arising from nasal mucous membrane transplanted to the anterior chamber of the eye and a cystic structure from homotransplanted fallopian tube. Similar findings were reported by von Tiesenhausen [10] with homotransplantation of epidermis and mucous membrane of embryonal chicken tissue, by Allen and co-workers [12] with anterior chamber transplantation of endometrium and by Berg [13] with intrarenal homotransplantation of ovarian tissue.

MATERIALS AND METHODS

Albino rats of the Wistar Institute Experimental Colony were used throughout. This colony has been maintained in our laboratory with no outbreeding for eight years, during which time group breeding has been practiced and no attempt made at brother to sister mating. The young adult female hosts weighed from 150 to 200 Gm. and the young adult male hosts from 210 to 260 Gm. The newborn donors were less than 24 hours old. The donors were killed with chloroform, dipped in 70 per cent alcohol and then in ether. Sterile technic was used throughout. The tissue was examined in sterile Ringer's solution under a dissecting microscope. When desired, the fallopian tube and bursa were teased from the minute kidney-shaped ovary.

Whole newborn ovaries, less than 1 mm. in each of two diameters, were transplanted under ether anesthesia. In testis transplantation, one-half testis was used. With a few exceptions right and left gonads were implanted in right and left eyes, respectively. Generally both eyes were used, and with a few exceptions like tissues were transplanted to the two eyes. The conjunctiva of the eye was grasped with a fixation forceps, and incisions 3 to 4 mm. wide were made with an angular keratome about 1 mm. inside the upper corneoscleral junction. Implantations were made with a modified 19 gage spinal puncture needle about 3 cm. long, with the plunger blunted and slightly longer than the barrel. Pressure on the cornea usually moved the tissue into the desired position in the lower angle of the eye. The rat receiving the implant was kept quiet for twenty minutes to prevent unnecessary trauma.

The eyes were examined at least once a week for six weeks and then twice a month. They were often completely free of hemorrhage and clouding at the end of one week. If growth occurred, it usually became evident at nine to fourteen days. Vaginal smears were followed in the cases of a number of normal and of spayed hosts.

9. Zahn, F. W.: Virchows Arch. f. path. Anat. **95**:369, 1884.
10. von Tiesenhausen, M.: Virchows Arch. f. path. Anat. **195**:154, 1909.
11. Goldzieher, W.: Arch. f. exper. Path. u. Pharmakol. **2**:387, 1874.
12. (*a*) Allen, E., and Bauer, C. P.: Surg., Gynec. & Obst. **47**:329, 1928. (*b*) Allen, E., and Priest, F. O.: ibid. **55**:553, 1932.
13. Berg, A.: Acta obst. et gynec. Scandinav. (supp. 3) **18**:1, 1938.

For serial transfer the excised eye was washed in sterile Ringer's solution. The tissue was removed from the anterior chamber, measured and examined. A fragment was taken for transplantation, and any remaining tissue was used for histologic study.

Most of the tissues were recovered two to six weeks (usually three to four weeks) after implantation. "Takes" were confirmed when microscopic sections showed identifiable mature gonadal tissue in a good state of health. When all the ovarian tissue was used for serial transfer or died before being removed from the eye at six weeks to eight months after implantation, definite gross follicles, corpora lutea, cyst formation, and estrus in the spayed females were used as criteria of successful grafts.

The animals were killed with chloroform. Postmortem examinations were made on all animals. Observations were made of the genital tract, and, when indicated, of the thoracic and abdominal organs and regional lymph nodes. Observations were also made for possible masculinization and feminization. Two rats of the 137 died of "rat pneumonia;" otherwise the findings were essentially negative.

The tissues were fixed in a 10 per cent solution of formaldehyde embedded in paraffin, sectioned at 5 to 6 microns and stained with hematoxylin and eosin.

HOMOTRANSPLANTATION OF THE OVARIES AND OF OTHER TISSUES OF THE NEWBORN RAT INTO THE ANTERIOR CHAMBER OF THE EYE

Percentage of Successful Transplants.—Altogether 273 transplants were made in 137 rats. Of the 273 transplants, 168 (61.5 per cent) were successful. Of the 137 rats, 109 (79.6 per cent) showed "takes." When ovary alone was transplanted into adult rats (normal and gonadectomized males and females), 40 of 67 tissues (59.7 per cent) "took." It will be noted that the success with grafts of newborn ovary with and without attached fallopian tube was closely comparable to the success attained in the series as a whole. Tissue implanted in spayed and in castrated rats showed a higher percentage of "takes" (about 73) than that implanted in normal males and females (about 43). Tissues implanted in rats treated with chorionic gonadotropin showed a slightly higher percentage of "takes" than did those in the similar untreated hosts and the highest percentage of "takes" in the series. Adult ovaries transplanted in 16 instances into spayed or castrated rats gave 6 "takes." Half-testis implants "took" well, although not as well as Turner's[14] series of transplanted whole prepuberal rat testes. Uterus or fallopian tube transplanted alone failed to grow well. Forty-six of 67 double adjacent tissue transplants were successful (tables 1 and 2).

Growth and Histologic Appearance of Transplanted Newborn Ovaries.—(*a*) In Normal Female and Male Hosts: The percentages of successful grafts in normal male and female rats were 40.0 and 46.7, respectively, which were only a little more than half the percentages

14. Turner, C. D.: Am. J. Anat. **63**:101, 1938.

observed in the spayed females and castrated males. In the normal hosts, both males and females, the growth of the transplants was slow and limited, with small and atretic follicles as seen in figure 2. Three of 7 ovarian tissues implanted in the males showed a tendency toward cystic degeneration of the small follicles.

TABLE 1.—*Homotransplants to the Anterior Chambers of Rats' Eyes*

Type of Transplants	Tissue "Takes"	Percentage
Newborn ovaries to normal and to spayed female and to normal and to castrated male rats	40 of 67	59.7
Newborn ovaries to other than normal or castrated adult rat hosts	11 of 18	61.1
Newborn ovaries to spayed female and castrated male hosts treated with chorionic gonadotropin	15 of 18	83.3
Newborn ovaries and attached fallopian tubes to normal and to spayed female and to normal and to castrated male rats	29 of 51	56.9
Newborn uterine horn tissues alone to normal and to spayed female rats	0 of 3	0.0
Newborn fallopian tube tissues alone to normal and to spayed female and to normal and to castrated male rats	3 of 6	50.0
Two adjacent tissues to normal and to spayed female rats, to normal immature female rats and to castrated male rats	46 of 67	68.7
Newborn half testes to normal and to spayed female and to normal and castrated male rats	15 of 23	65.0
Adult ovaries to normal and to spayed female rats and to castrated male rats	6 of 16	37.5
Fetal ovaries to a spayed female rat and a castrated male rat	3 of 4	75.0
Total	168 of 273	61.5

TABLE 2.—*Analysis of the Growth of Transplanted Newborn Rat Ovaries in Four Types of Adult Rats*

Hosts	"Takes"	Percentage of "Takes"	Average Weight of Tissue at 25 Days	Characteristic Growth
Normal adult females	6 of 15	40.0	1.3 mg. (0.6, 1.5, 1.8 mg.)	Slow growth; small follicles with tendency to degenerate
Normal adult males	7 of 15	46.7	2.5 mg. (1.6, 2.3, 3.6 mg.)	Slow growth as in normal female; tendency (3 of 7 tissues) to become cystic
Spayed adult females	13 of 18	72.2	12.3 mg. (5.6, 7.6, 9.3, 26.6 mg.)	Rapid growth; complete round corpora lutea, usually large; small amount of follicular tissue
Castrated adult males	14 of 19	73.7	11.0 mg. (1.4, 3.5, 11.2, 15.0, 23.7 mg.)	Rapid growth; stimulation of granulosa cells to form abnormal patterns, folliculoid and polypoid

(*b*) In Spayed Female and Castrated Male Hosts: The percentages of "takes" in the spayed female and castrated male rats were almost equal in our series (72.2 and 73.7, respectively). Rapid growth and early maturation of tissue were characteristic of the transplants in these hosts. Ovarian grafts grew as well in the male host deprived of testes as in the female host with ovaries removed. In the spayed female complete round corpora lutea, usually large, made up the mass of the graft,

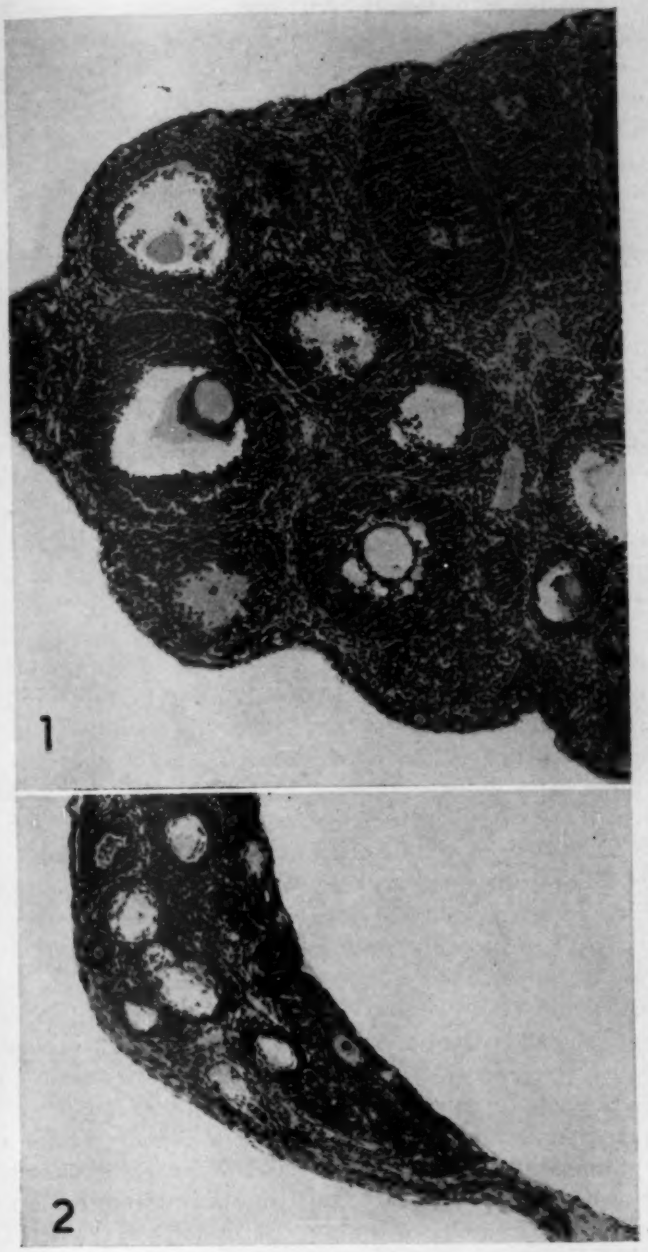

Fig. 1.—Normal ovary from a 25 day old rat (× 110). Follicles are numerous, but no corpora lutea have formed.

Fig. 2.—Newborn ovary transplanted to the eye of a normal male rat six weeks previously (× 110). The follicles are small and frequently atretic. Transplants in the normal female show similar development.

but relatively normal follicular tissue was also present (fig. 3). The microscopic appearance of this tissue resembled normal adult ovary except that the corpora lutea were not always as large and the follicular tissue often showed a slightly abnormal pattern. Corpora lutea were usually present in grafts removed at twenty-four days and probably developed much earlier in spayed hosts, which showed estrous smears as early as nine days after implantation. Corpora lutea develop at a much later period in normal animals. Transplanted ovaries in the castrated male host showed follicles with a tendency to become slightly cystic and an apparent stimulation of granulosa cell growth in an abnormal pattern (fig. 4), similar to but more conspicuous than that seen occasionally in the other hosts. There was a folliculoid or even polypoid arrangement of granulosa cells, which sometimes grew in spur formation into the lumen of the follicle. Small areas of these grafts resembled histologically granulosa cell tumors of the human ovary.

The weights of tissues removed from twenty-four to twenty-six days (usually twenty-five days) after implantation and proved healthy by microscopic examination were compared with a control standard previously prepared from the weights of the ovaries of 35 rats 25 days old. Ninety-five per cent of the control values for the combined weight of both ovaries ranged between 8.1 and 15.7 mg. (average, 11.9 mg.); a range of 4.05 to 7.85 mg. has been used for the weight of one ovary. The weights of the transplants varied greatly. The average weight of the ovarian transplants in the normal male hosts was about twice that found in the normal female hosts but all the values fell below the control group. On the other hand, 2 of the 4 tissues from the spayed females and 3 of the 5 from the castrated males exceeded the upper limit of the control value for 25 day old rats and 2 attained a weight three times that value (table 2). The great difference in growth stimulus between the normal and the spayed or the castrated hosts can be seen by examining figures 2, 3 and 4 (all of the same magnification) and by comparing with a normal ovary from a 25 day old rat (fig. 1).

(*c*) In Other Hosts: It was thought that the growth of newborn ovaries, which followed definite lines in the four types of adult hosts discussed in the foregoing paragraphs, might be significantly different in young animals or in adult animals of abnormal endocrine status. Ovarian and testicular implants in 3 puberal females at the time of opening of the vagina did not show essential differences from such tissues growing in normal adult hosts. Four transplants were made to 2 old female rats which had shown constant estrus for several weeks. One of the 2 transplants which "took," although somewhat degenerate, showed areas resembling the slightly cystic follicles and abnormal granulosa cell pattern characteristic of the transplant in the castrated male host. Two of 4 newborn ovaries transplanted to 2 old female rats

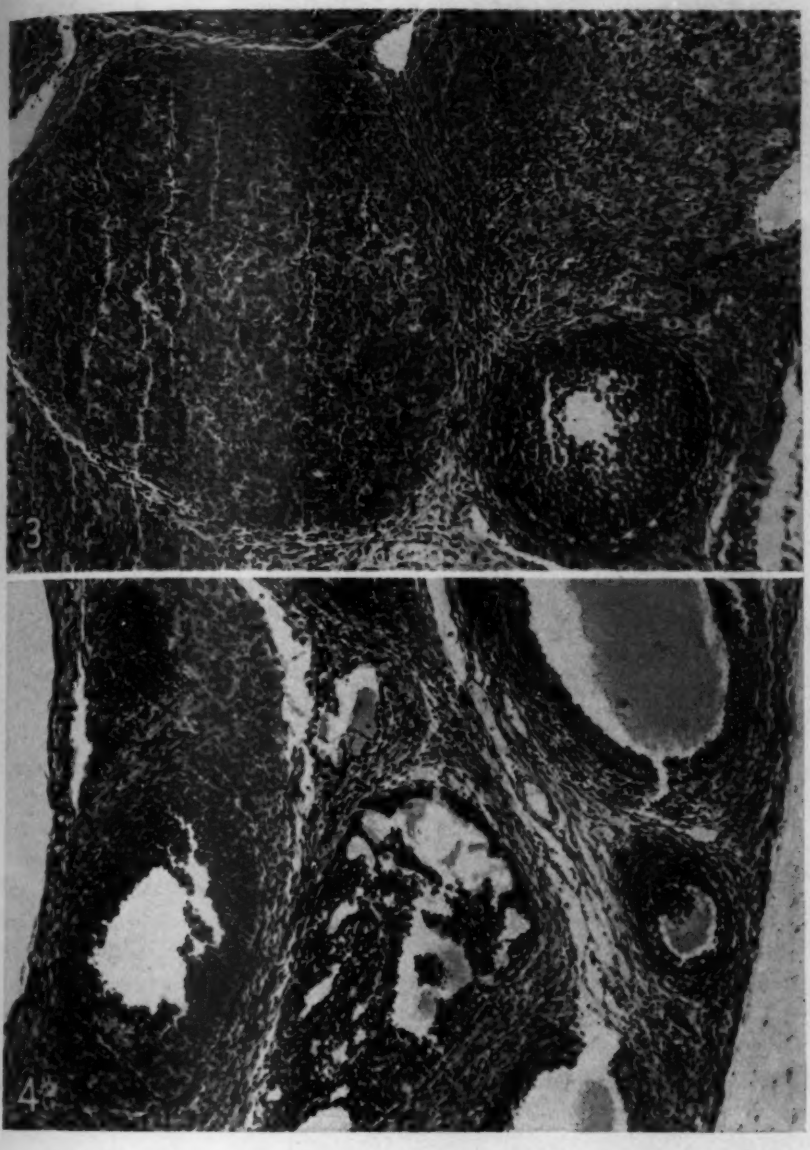

Fig. 3.—Newborn ovary transplanted to the eye of a spayed female rat four weeks and five days previously (× 110). Corpora lutea form the main mass of the tissue, although relatively normal follicles are also present.

Fig. 4.—Newborn ovary transplanted to the eye of a castrated male rat three weeks previously (× 110). Cystic follicles and a stimulation of granulosa cells are shown. The magnifications in figures 1 to 4 are the same. The small mass shown in figure 2 indicates a less than normal stimulus to growth, while the mass in figure 3 and that in figure 4 indicate a stimulus far greater than normal.

in more or less constant diestrus showed gross "takes" but grew slowly and were dead at three and four months. Tissue "takes" in 1 of 3 sterile female rats showing diestrous smears were like those in a normal adult female host. The transplanted tissue in another showed grossly a sudden increase in size at five weeks and resembled the response in the spayed female host; on removal at six weeks it showed follicles and degenerate corpora lutea. The transplant in the third rat failed to "take." The transplants did not affect the course of the vaginal smears of noncycling rats.

(*d*) In Spayed Female and Castrated Male Rats Treated with Chorionic Gonadotropin: Daily subcutaneous injections of chorionic gonadotropin were given to adult spayed females and adult castrated males three to fourteen days before implantation and usually during the early days of the establishment of the grafts. The number of injections ranged from fourteen to twenty (fourteen days in 7 of 9 rats). The tissues were recovered between three and four weeks after transplantation. Neither these differences nor the interval elapsed since spaying or castration nor the stage of the vaginal cycle led to conspicuous variations in the histologic appearance of the graft. Of the 5 spayed female rats, 1 received daily injections of 20 rat units, 2 of 40 and 2 of 100 rat units of chorionic gonadotropin (antuitrin S [15]). Eight of 10 eyes showed successful grafts. Of the 4 castrated male rats, 2 received daily injections of 20 and 2 of 40 rat units. Seven of 8 eyes showed successful grafts. A total of 15 of 18 transplants grew.

The microscopic appearance of the newborn ovaries in spayed female rats treated with chorionic gonadotropin differed distinctly from that of such transplants in untreated spayed rats. No large corpora lutea were observed, but lutein cells were present at the border of the follicles and in the stroma. The centrally situated granulosa cells were arranged in a polypoid or folliculoid pattern (fig. 5). Follicular tissue was far more prominent than in the untreated spayed female rat, and its growth appeared to be stimulated. At a dose of 40 rat units the luteinized cells appeared slightly smaller than at a dose of 20 rat units. The 3 tissues recovered after treatment of the hosts with 100 rat units showed degenerate masses of follicles and luteinized and inflammatory cells. It is uncertain whether or not this finding was due to the large dose of chorionic gonadotropin. In general, the transplants resembled in growth and microscopic character those in the castrated males, either untreated or treated with chorionic gonadotropin.

Although chorionic gonadotropin definitely changed the type of growth in the spayed female rat, it did not appear to affect it in the castrated male.

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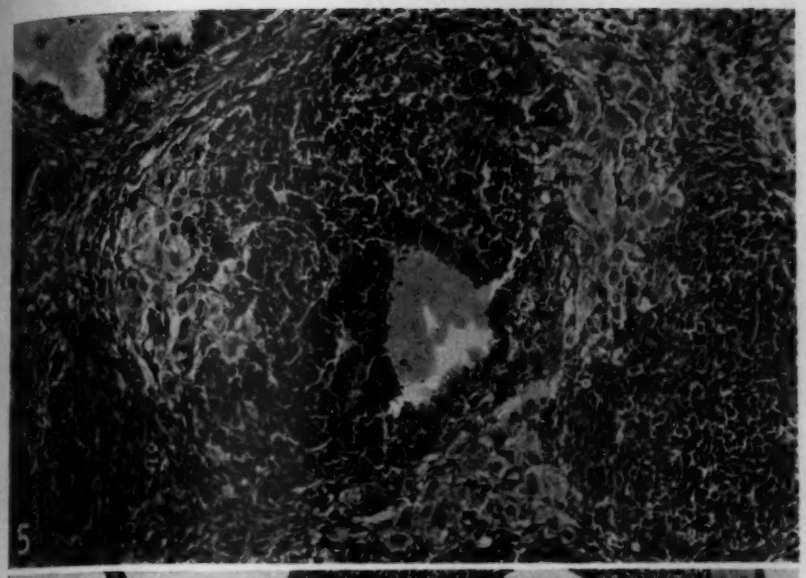
15. Antuitrin S, Parke, Davis & Co., was used.



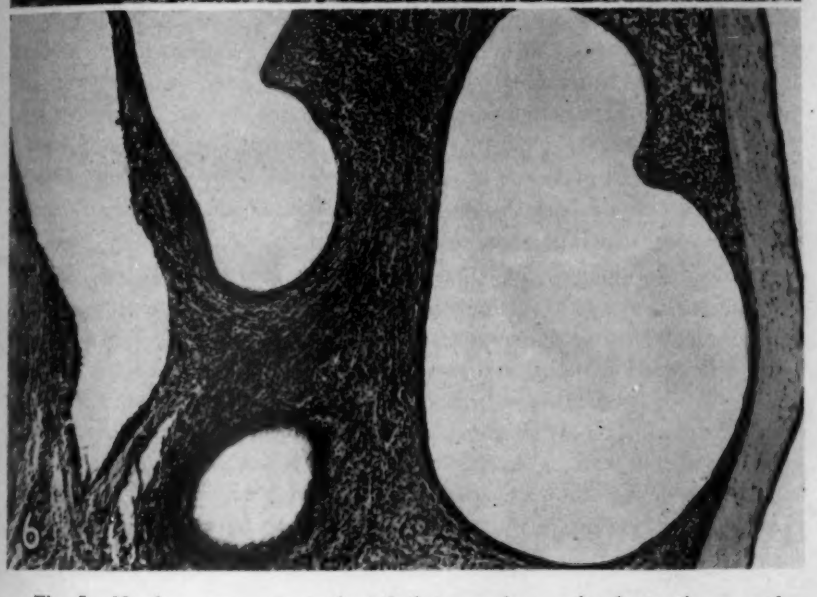


Fig. 5.—Newborn ovary transplanted three weeks previously to the eye of a spayed female rat that had been treated with daily doses of 20 rat units of chorionic gonadotropin (× 155). Granulosa cells with a polypoid type of growth are surrounded by luteinized cells.

Fig. 6.—Newborn ovary and fallopian tube transplanted to the eye of a normal female rat two weeks previously (× 65). Structures arising from tube predominate over ovarian tissue. Note the loss of folds in the section of tube below and the cuboidal epithelial lining of the cystic sections of tube. In some instances a single "cyst" filled almost the entire anterior chamber of the eye. The cornea appears at the right of the figure.

Adjacent Transplants of Two Newborn Tissues in the Same Eye.—It seemed of interest to observe the possible influence on one another of different glandular tissues growing adjacently in the same environment. Tissues were placed separately in the eye of a spayed or a castrated rat and moved to the inferior angle. They frequently touched each other and often could be seen growing individually. Successful "takes" were observed in 46 of 67 eyes.

The following observations were made: When newborn ovary and half-testis were implanted, either one or both of these tissues grew. When both "took," they either grew separately or closely intermingled, resembling an ovotestis. Tubal tissue gave rise to cystic structures. Two tissues grew adjacent to one another without influencing the histologic picture of either. They were more often degenerate and invaded by fibrous tissue than tissues implanted alone. Newborn adrenal, renal cortex, submaxillary gland and upper part of the intestine implanted with newborn gonads were not recovered. Newborn gonads and structures arising from fallopian tube appeared either to "take" more readily or to overgrow the other tissue. Two newborn ovaries freed from the fallopian tubes "took" as well or better than one ovary alone. Regardless of the close intermingling of their growth or of whether they were from littermate sisters or not, the ovaries did not appear to influence each other's development. Healthy grafts were recovered from 4 of 5 eyes of normal females, 4 of 5 eyes of spayed females and 2 of 2 eyes of castrated males. In spayed female rats double ovarian grafts produced regular estrous cycles which persisted for more than six months.

It was thought possible that the presence of a like tissue which had become partly necrotic through autolysis might exert some effect on the development of freshly removed newborn ovaries. Newborn ovaries were submitted to autolysis in physiologic solution of sodium chloride at 37 C. for twenty-four to forty-eight hours and transplanted with fresh ovaries to 2 normal and 2 spayed rats. Both tissues grew in one eye of a normal rat. When the tissue was removed at eighteen weeks, histologic section showed small follicles and three clearly demarcated corpora lutea. This is the only instance in which corpora lutea were found in a transplant to a normal female rat. No other effect of the close association of autolyzed and fresh tissue transplants was ascertained.

Although some double transplants were kept for long periods to allow for abnormal developments, none of these experiments lent support to theories implicating fetal rests or necrosis in the genesis of abnormal growths.

Attempts to Transfer Newborn Ovarian Tissue in Series.—Thirty-two attempts were made to transfer in series newborn ovaries which

had been successfully transplanted in 8 adult hosts of various types. The tissues were transferred three to four weeks after transplantation. Two transplants were successfully carried in spayed females, a third in castrated males. One graft, transferred from the original spayed host, "took" in both eyes of the second host (series 1) and subsequently in 3 of 4 eyes (series 2). Another transplant was successful in both eyes of a spayed female (series 1) but failed to transfer to 2 other rats. Gross "takes" were confirmed by the onset of estrous smears eight and nine days after transplantation.

In the castrated males 1 of 2 transplants was successful in the second host (series 1), and 3 of 4 "took" in the next transfer (series 2). The criteria of gross "takes" in both male and female rats were increase in size of the tissue, a pink, healthy color, hemorrhagic spots and follicle formation. Attempts at third serial transfers of these tissues failed.

The growth potentialities did not appear to increase with transfer. The use of littermate sisters for successive hosts did not increase the success of the serial transfers.

Estrous Smears of Female Rats Carrying Ovarian Transplants.—Spayed rats carrying transplanted newborn ovaries free of fallopian tubes went into estrus at nine, eleven, eleven, thirteen, sixteen, nineteen and twenty-six days, respectively, and 4 spayed animals with successfully transplanted ovaries with tubes were all in estrus at twenty days or earlier. The first estrus occurred independently of the time elapsing between spaying and transplantation. Had the ovary been left in situ, the donor would have been expected to be in estrus at about 70 days of age and not earlier than 45 days. The early appearance of estrus (at nine days) shows the remarkably early maturation of immature ovarian tissue in the adult spayed rat. Certain animals have shown regular cycles for more than twelve months. When charted, these cycles often cannot be distinguished from the cycles of normal females. In other cases changes in the transplant were associated with variations in the vaginal smear. For example, the development of constant estrus appeared to accompany degeneration of the transplant. Estrous cycles of normal female rats with living transplants did not show significant changes. Spayed females with successful grafts of adult ovaries began cycles at seven, ten and fourteen days. This was anticipated since the ovarian tissue was already mature. However, there was a tendency to prolonged estrus and lengthening of the cycle to twelve to fourteen days. In 2 of 3 hosts treated with chorionic gonadotropin the first estrous phase after operation was prolonged to as much as twelve days.

Structures Arising from Transplanted Fallopian Tube.—In order to avoid trauma to the small delicate newborn ovary, we first implanted the ovary with the attached fallopian tube and bursa and occasionally the

tip of the uterine horn. Twenty-nine of 51 transplants grew. In 50 per cent or more of successful transplants in normal and gonadectomized female and male hosts thin-walled, bubble-like cysts developed. The type and extent of the development of these locules were the same in each type of host. These cysts apparently overgrew ovarian tissue and varied in size from barely visible structures to locules which nearly filled the anterior chambers and measured as much as 5 by 4 by 2 mm. They contained clear fluid. Microscopic examination showed a round or oval lumen lined by cuboid cells of varying height. The ovarian tissue was frequently degenerate and less healthy than when transplanted alone. In tissue in which barely visible locules were seen, microscopic examination showed relatively undilated loops of fallopian tube adjacent to dilated cystic loops (fig. 6).

Since it was believed that these cystic structures arose from fallopian tube, 3 transplants of newborn uterine horn and 6 transplants of fallopian tube were made to different hosts. In general, these transplants either failed to "take" or showed transient evidence of growth. However, one fallopian tube transplant grew in a normal female rat, produced a thin-walled cyst lined by tall cuboidal epithelium and resembled in every way the cystic structures arising from implantation of tube and ovary.

CONTROL STUDIES

Tissues Removed More Than Six Weeks After Transplantation.—Tissues were usually removed between two and six weeks after operation. However, 24 of 46 transplants (52.2 per cent) left in the eye for from seven weeks to sixteen months were successful. Healthy ovarian tissue persisting six and twelve months after transplantation still produced regular cycles in 2 spayed females; in 4 others the smear became diestrous in five to nine weeks.

Ovarian tissue in a castrated male rat four months after transplantation showed a histologic picture similar to that of tissues removed earlier except that the follicles were lined with fewer layers of granulosa cells. There was metaplasia of follicular to cuboidal epithelium in some areas. No corpora lutea were present.

Intervals Between Gonadectomy and Transplantation.—Seventy rats were gonadectomized before transplantations were made to the anterior chambers of the eyes. Sixteen males and 28 females were gonadectomized six to eight days, 14 females and 12 males eight to forty days, prior to transplantation. In general, the percentage of "takes" and the rapidity of growth did not appear to vary significantly.

Transplanted Adult Ovaries.—Fourteen of 16 adult ovaries were transplanted in spayed or castrated rats. There were 6 "takes" (37.5 per cent). With the mature ovaries a smaller percentage of "takes"

was obtained, and the growth was not as great as that of newborn ovaries. The transplanted tissues when removed from spayed female hosts consisted mainly of corpora lutea resembling those arising in newborn ovaries transplanted to similar hosts. In castrated males the abnormal pattern was less striking with adult than with newborn ovary transplants.

Fetal Ovaries Transplanted to Adult Rats' Eyes.—Fetal ovaries removed on the eighteenth day of gestation (three to four days before term) were transplanted to a spayed and a castrated host. Double ovarian transplants were made in the spayed female host and a single one in each eye of the castrated male. In fifteen days estrous cycles appeared in the spayed female and showed a tendency to be prolonged. At twenty-five days the tissue resembled that obtained from a spayed female treated with chorionic gonadotropin. The transplanted fetal ovary removed from the male host resembled histologically a transplanted newborn ovary.

Newborn Gonads Transplanted to Other Sites.—Ten newborn gonads were transplanted to adult testes or to ears, but the transplants did not grow as well as those in the anterior chambers of eyes.

COMMENT

Most malignant growths in man occur at the period of life when there is an alteration of hormonal balance and often a manifest lack of one or more hormones. It is therefore suggested that in certain persons who are possessed of cells of embryonal, fetal or other type with marked potentialities for growth there may be a stimulation which results in neoplastic disease of a benign or a malignant character. In view of the possibility that ovarian tissue growing in an abnormal hormonal environment might develop in an aberrant manner, ovaries of newborn rats have been transplanted into the anterior chambers of the eyes of adult rats under varying hormonal conditions. The ovarian tissue of newborn rats was chosen because it is not only immature tissue but has definite embryonic characteristics which might make it more susceptible to change. Primordial follicles are rare, and there is a predominance of primordial ova, as shown in figure 7.

It is obvious from our observations that transplanted newborn ovarian tissue has greater potentiality for growth than transplanted adult tissue. It is also apparent that this potentiality for growth is manifest to a greater degree when the physiologic hormonal relationship is disturbed by removal of the gonads. In normal adult male hosts 7 of 15 transplanted newborn ovaries grew, and in female hosts, 6 of 15. In gonadectomized hosts the percentage of "takes" was almost doubled; 14 of 19 transplants "took" in the castrated male hosts and 13 of 18 in

the spayed females. It is of interest that the transplants grew as well in the hosts deprived of ovaries as in those deprived of testes. This stimulation might be attributed either to the lack of effect of gonadal hormones on the transplant or to the effect of removal of gonadal hormones on the hormone production of the pituitary.

In the normal hosts, male or female, the growth of transplants was slow and limited and the tissue showed small and atretic follicles (fig. 2). Transplants in gonadectomized hosts were characterized by markedly rapid growth and early maturation of the ovarian tissue. In the spayed

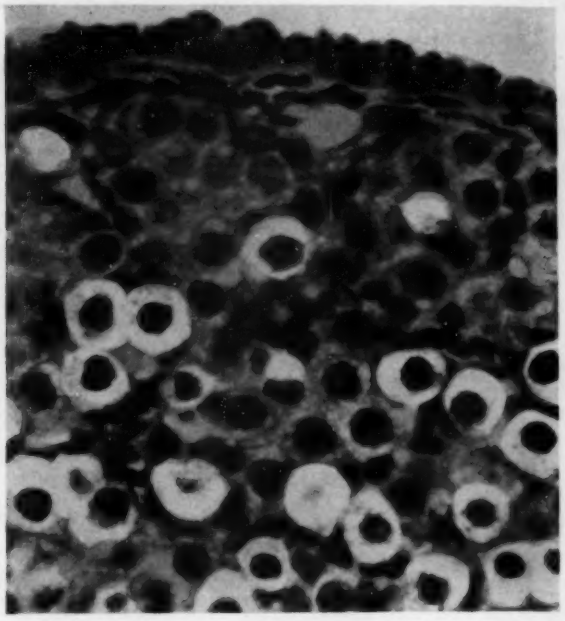


Fig. 7.—Normal ovary from a newborn rat (× 325). This tissue was used in the transplants. The germinal epithelium and numerous primordial ova are seen. Primordial follicles are rare.

female hosts transplants resembled normal adult ovarian tissue rather than tissue of the same chronologic age and showed well formed corpora lutea and smaller amounts of follicular tissue (fig. 3). These findings are similar to those reported by May [5] with 3 day old rat ovaries and by Goodman [4] with immature ovaries transplanted into the anterior chambers of the eyes of spayed females. Lipschütz [16] found that large

16. Lipschütz, A.: Die experimentellen Grundlagen der Eierstocksverpflanzung, Budapest, R. Novak & Co., 1930.

graafian follicles with corpora lutea were almost always present in guinea pig ovaries homotransplanted to the kidneys of spayed females but observed widening of the graafian follicles with preservation of the granulosa cell layer and absence of corpora lutea in similar transplants in castrated male hosts. In this study, with newborn rat ovaries in castrated male hosts there was a tendency toward the formation of cystic follicles together with a stimulation of the granulosa cell growth in an abnormal pattern which was seen only occasionally and less definitely in the other hosts (fig. 4). There was a folliculoid or even polypoid arrangement of the granulosa cells, which sometimes grew in spur formation into the lumen of the follicle. Small areas of these grafts resembled histologically the human granulosa cell tumor of the ovary. The latter observation suggests the possibility that if there were excessive stimulation neoplastic disease might arise.

Chorionic gonadotropin was given to gonadectomized hosts prior to transplantation of the newborn ovaries and during the early period of the establishment of the grafts. This treatment did not alter the picture of tissue growth in the castrated males, but in the spayed females there was an interference with the formation of corpora lutea that was characteristic of the transplants in these hosts, with stimulation of the growth of granulosa cells and the appearance of large luteinized cells in the border of the follicle and in the stroma (fig. 5). These findings resemble those described by Deanesly [17] in association with the androgenic activity of ovarian grafts in the ears of castrated male rats. In general, the histologic picture of transplants in the hosts treated with chorionic gonadotropin may be said to approach that characteristic in the castrated male. Dantschakoff [18] reported stimulation of follicles of the ovary of the newborn guinea pig treated prenatally with testosterone propionate; the ovary showed four to eight weeks' development, with ripe follicles having a thick granulosa cell layer with numerous Call-Exner bodies.

Observation of transplants in other hosts, of varying endocrine states (puberal, constant diestrous, constant estrous and sterile females), indicated that such states did not influence significantly the growth character of the transplants. The length of time elapsing before the removal of the tissue did not alter the histologic picture of surviving transplants. Other tissues, either like or unlike, transplanted adjacent to newborn ovaries did not seem to produce an abnormal stimulus.

The transplants of immature ovarian tissue not only grew but showed rapid maturation and early functional activity. Vaginal smears followed daily in the cases of spayed females indicated that the transplanted tissues

17. Deanesly, R.: Proc. Roy. Soc., London, s.B **126**:122, 1938.

18. Dantschakoff, V.: Ztschr. f. Zellforsch. u. mikr. Anat. **29**:214, 1939.

had matured as early as nine days after implantation, whereas in situ they would have matured at about 70 days of age and not earlier than at 45 days. These cycles often proceeded in a regular and normal manner and sometimes for as long as one year. Pfeiffer [19] reported estrus at twelve to sixteen days in spayed rats carrying intrarenal grafts of newborn rat ovaries, and May [5] obtained estrus smears in thirteen to twenty-seven days in the cases of spayed rats with anterior chamber transplants of 3 day old rat ovaries.

In a small series, fetal ovaries transplanted to gonadectomized hosts responded by rapid maturation and resembled histologically the newborn ovaries growing in spayed females treated with chorionic gonadotropin.

Serial transfer of transplants of newborn ovary has been accomplished. It did not appear to alter the tissue's response or to increase the potentiality for growth.

It was of interest that fragments of fallopian tube transplanted with the newborn ovary to the normal or the gonadectomized host, male or female, produced thin-walled, bubble-like cysts, which tended to overgrow the ovarian transplant and often filled the anterior chamber of the eye (fig. 6). Goldzieher [11] described cystic structures arising from nasal mucous membrane and from the fallopian tube. Von Tiesenhausen [10] observed a tendency of homotransplants of epidermis and mucous membrane of embryonal chicken tissue to form small cysts. Allen and Bauer [12a] and Allen and Priest [12b] observed that endometrium transplanted to the anterior chamber showed a marked tendency to proliferate, secrete and produce glandlike spaces and cystic cavities. Berg [13] mentioned cysts probably arising from tubal constituents in intrarenal homotransplanted adult ovaries of mice.

Except for the atypical stimulation of the granulosa cell layer in the transplants in the castrated male hosts, which resembled in some areas human granulosa cell tumors, no unusual growth pattern has been obtained by transplanting immature ovarian tissue into an abnormal environment. Apparently any existing embryonal rests or other tissues with unusual growth potentialities in these transplants are not stimulated to abnormal growth by either the endogenous hormonal stimuli or the exogenous chorionic gonadotropin of these experiments.

SUMMARY

The homotransplantation of newborn rat ovaries to the anterior chambers of eyes was successful in a definitely higher percentage of gonadectomized than of normal rats. In gonadectomized hosts rapid growth and early maturation of ovarian tissue often exceeded by four

19. Pfeiffer, C. A.: Proc. Soc. Exper. Biol. & Med. **31**:479, 1934.

or five times that expected with the ovary growing in situ. The histologic development in various types of adult hosts was specific for each type, different normally occurring ovarian structures being favored in each case. In castrated male hosts granulosa cells were subject apparently to an unusual growth stimulus. In spayed females the grafts showed well formed corpora lutea, but in corresponding hosts treated with chorionic gonadotropin the grafts showed an atypical histologic pattern. The serial transfer of newborn rat ovary in gonadectomized hosts did not increase the potentialities of this tissue for growth. The development of cystic structures from homotransplanted pieces of fallopian tubes of newborn rats suggested the possibility that mucous membrane transferred to an abnormal environment may be liable to cystic degeneration.

POLIOMYELITIS INDUCED BY THE LANSING STRAIN OF VIRUS

A COMPARISON OF LESIONS IN MAN AND IN MONKEYS

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BETHESDA, MD.

The Lansing strain of poliomyelitis virus has attained considerable prominence in the past two years because it is the first strain of virus definitely established as infecting mammals below the primates. Armstrong,[1] in 1939, was the first to report the successful transfer and propagation of this strain of virus in the eastern cotton rat. Subsequently in 1939, Armstrong [2] reported its further transfer to albino mice, and Armstrong and Lillie [3] described the pathologic picture of the disease so produced in these animals. In the course of this work, there accumulated a number of monkey brains which had been infected with this virus. From a study of such tissues, some infected with virus before and some with virus after rat passage, Peers [4] published a note on the general pattern of disease induced in monkeys by the Lansing strain and concluded that serial passage of this strain through rats had not visibly altered the character of disease produced by the virus.

Recently, the National Institute of Health has been fortunate in obtaining from Dr. Max M. Peet and Dr. Konstantin Lowenberg-Scharenberg of the University of Michigan the remaining portion—about two thirds—of the human brain from which the Lansing strain was first isolated, with an abstract of the clinical history. So far as can be ascertained, there has been no detailed topographic study of the pathologic changes of poliomyelitis in the human tissues from which present laboratory strains of virus have been isolated, and very little topographic record of the pattern of disease induced by such strains in monkeys. Material now available makes it possible to compare the pathologic pattern of the spontaneous disease in the human subject with that

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From the Division of Pathology, National Institute of Health.

This work was sponsored by a grant from the National Foundation for Infantile Paralysis, Inc.

1. Armstrong, C.: Pub. Health Rep. **54**:1719, 1939.
2. Armstrong, C.: Pub. Health Rep. **54**:2302, 1939.
3. Lillie, R. D., and Armstrong, C.: Pub. Health Rep. **55**:718, 1940.
4. Peers, J. H.: Pub. Health Rep. **55**:726, 1940.

produced in monkeys by virus isolated from the tissue of that subject. Because of the absence of such comparative studies, and because of the unique properties of the Lansing strain, the following description of the disease caused by this strain in man and in monkeys is offered.

CLINICAL NOTE

The patient whose brain is the subject of this report was a 19 year old white youth, a resident of Lansing, Mich. Seven years prior to his final illness he had suffered attacks of measles and chickenpox and had undergone tonsillectomy and adenoidectomy. Four and a half months before his final illness he was operated on for acute suppurative appendicitis and had made a complete recovery. During and following his attack of appendicitis, several members of his immediate family presented severe sore throat, fever and a questionable rash.

Aug. 22, 1937 the patient became ill with headache and dizziness, difficulty in swallowing and repeated vomiting. His condition became worse, and after forty-eight hours he entered the hospital. Physical examination on admission revealed an acutely ill young man with a temperature of 104 F., a pulse rate of 110, and a respiratory rate of 32 His eyes showed slight lateral nystagmus but were otherwise normal. His mouth drew slightly to the left as he showed his teeth. The tongue protruded in the midline, with only a fine tremor. The pharynx was injected, and swallowing was difficult. The limbs showed no paralysis or change in reflexes, and no abnormal reflexes were present. Some twitching of the muscles of the limbs appeared, but actual paralysis is not mentioned in the record. Paralysis of the muscles of respiration developed, and the patient died on the morning of the fourth day of illness. The heart continued to beat for two or three minutes after breathing had ceased.

At autopsy the brain was edematous and markedly hyperemic. On section the gray matter, especially that of the basal ganglions, brain stem and cord, was intensely congested, so that grossly it had a purplish red color and presented numerous small perivascular hemorrhages. The original histologic preparations showed marked inflammatory changes, especially in the medulla, characteristic of poliomyelitis.

COMPARISON OF SPONTANEOUS HUMAN AND INDUCED MONKEY DISEASE

Cerebral Cortex.—Figure 1 *A* displays the general distribution of lesions in the cerebral cortex of man (left) and monkey (right). In all diagrams the same symbols are employed to represent types of lesions. Perivascular round cell infiltrations are designated by small circles. Foci of inflammatory cells, chiefly microglia, in the parenchyma are shown by groups of dots. Dead cells are indicated by crosses. Only recognizable necrotic cell bodies are recorded as dead cells. Total disappearance of neurons when extensive is noted, but it is felt that vacuoles in ground substance and focal microglioses do not always mark the former position of vanished cells.

A total of 30 blocks of cerebral cortex, out of the 46 usually taken, were obtained from the remaining portions of the Lansing brain. These

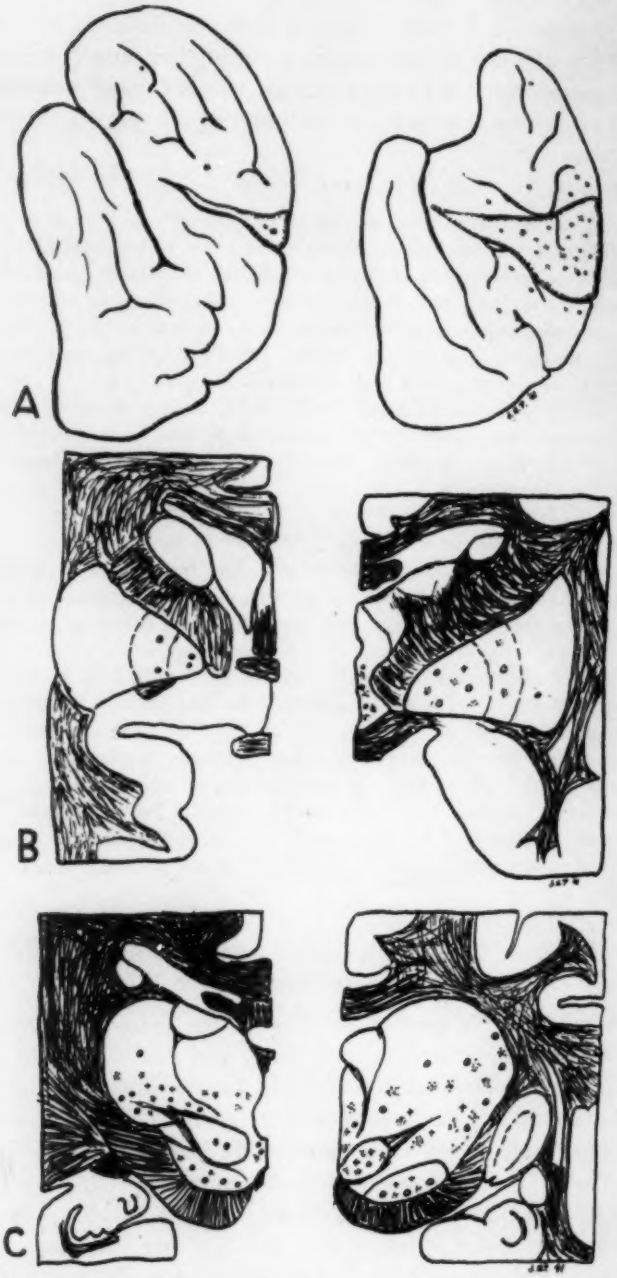

Fig. 1.—*A*, cerebral hemispheres; of man (left) and monkey (right). *B*, corpus striatum; *C*, level of thalamic nuclei. Small circles represent perivascular round cell infiltrations; groups of dots, foci of inflammatory cells, chiefly microglia; crosses, dead cells. The same symbols are employed in all the figures. In all the figures man is represented on the left and the monkey on the right.

comprised one or more blocks from each lobe of the cortex. The right side of the brain was more completely represented. In all the cortex, only two inflammatory lesions were found. These consisted of small foci of mobilized microglia deep in the cortex; one was in the posterior end of the right second frontal convolution and the other in the precentral convolution near the vertex. An unusual feature throughout the cortex was the extreme venous congestion, often with large pools of hemorrhage greatly distending perivascular spaces. This hemorrhage was apparently agonal, as there was no trace of cellular reaction to the effused blood, and it may have been the result of the circulation's continuing for several minutes after respiration had ceased. The subarachnoid space showed a scarcely perceptible increase of large mononuclear cells.

The lesions in the cortex of the monkey shown in figure 1 *A* are a composite average based on examination of 12 or more large transverse blocks from the cerebral hemispheres of each of 23 rhesus monkeys used for isolation and passage of the Lansing strain of virus. These were all killed when paralysis was well developed, usually about the eighth day after inoculation. As in the human brain, the inflammatory lesions were strikingly concentrated in and about the motor cortex. They were more extensive, corresponding to the considerably greater expanse of motor type cortex, in the monkey brain. They were also much more severe, possibly because nearly all the animals were inoculated by a direct injection of the virus into the parietal lobe. Slight to moderate round cell infiltration was observed about scattered cortical vessels, and patches and streaks of microgliosis were present in almost all the brains, on the opposite as well as on the inoculated side. Coagulation necrosis and occasional neuronophagia of Betz cells were observed in about 20 per cent of the brains examined. These more severe changes did not accumulate in the animals at the end of the passage series but were scattered at random throughout. Lesions were practically confined to the frontal and parietal lobes; rarely a few scanty perivascular collars appeared in the inferior part of the temporal cortex. No definite lesions were ever observed in the occipital lobes. Nothing approaching the extreme congestion and perivascular hemorrhage of the human tissue appeared in the monkey. Congestion was only moderate, but there was fairly constantly a small deposit of hemosiderin in macrophages in perivascular spaces of the subcortical white matter. Round cell infiltration in meninges, frequently concentrated about veins, was a prominent feature, but a good deal of it may be attributable to the trauma of intracerebral inoculation.

Corpus Striatum.—Figure 1 *B* presents the distribution of inflammatory changes in the corpus striatum at the level of the optic chiasm.

At this level also lesions were less numerous and less severe in man than in the average monkey. Unfortunately, a large part of the human tissue from this region was missing. The remaining portions showed scattered perivascular collars in the globus pallidus and periventricular gray matter and a single loose aggregation of microglia and rare polymorphonuclears in the lateral edge of the right caudate nucleus. No damage to nerve cells was demonstrable. Throughout the corpus striatum, as in the cortex, venous congestion was extreme, and there were large perivascular hemorrhages without cellular reaction.

In the monkey, evaluation of the damage in the striatal and thalamic regions was complicated somewhat by the area of necrosis, often large, caused by the mechanical and chemical injury of intracerebral inoculation. This area was marked by massive foam cell reaction, proliferation of capillaries and thick mantling of neighboring vessels by round cells. Excluding such changes, there appeared quite constantly a moderate perivascular infiltration, scattered small compact foci of mononuclear cells (microglia) and occasionally a few necrotic nerve cells in the medial part of the globus pallidus and the periventricular gray matter. In a few animals the adjacent putamen presented an occasional scanty perivascular collar or a small loose aggregation of microglia. Degenerative changes in nerve cells were not observed. The nearby caudate nucleus and its terminal enlargement in the amygdaloid nucleus remained strikingly free of visible damage. In only 1 animal were these nuclei found to have focal and perivascular infiltrations independent of the inoculation trauma.

Thalamus.—At the level of the thalamic nuclei, as shown in figure 1 *C*, the lesions in man and in the average monkey seemed to be approximately equal in extent and severity. In both there was a distinct accumulation of inflammatory changes in the ventral and lateral portions of these central masses of gray matter. In addition to focal and perivascular accumulations of inflammatory cells, rare necrotic cells, some undergoing neuronophagia, were observed in the human brain and in about one third of the animal brains.

The scarcity of lesions in two structures seen at this level is worthy of note. Sections of two levels from each side of the human hippocampus showed no lesions of any sort. In the monkeys, mild lesions in the form of slight perivascular and focal infiltrations were found in the hippocampus of 5 of 23 brains examined. No necrosis of neurons was seen.

Sections of the human lateral geniculate body were not available. As regards the monkeys, a lesion with necrosis of a few cells was noted in the lateral geniculate body in 1 of 6 brains, but quite possibly the

injury resulted from inoculation trauma. No lesions appeared in the claustrum in either the human or the animal specimens.

Midbrain.—In figure 2 *A* is shown the distribution of lesions in the midbrain at the level of the oculomotor nuclei. In both man and monkey almost all the gray matter at this level was damaged to some degree,

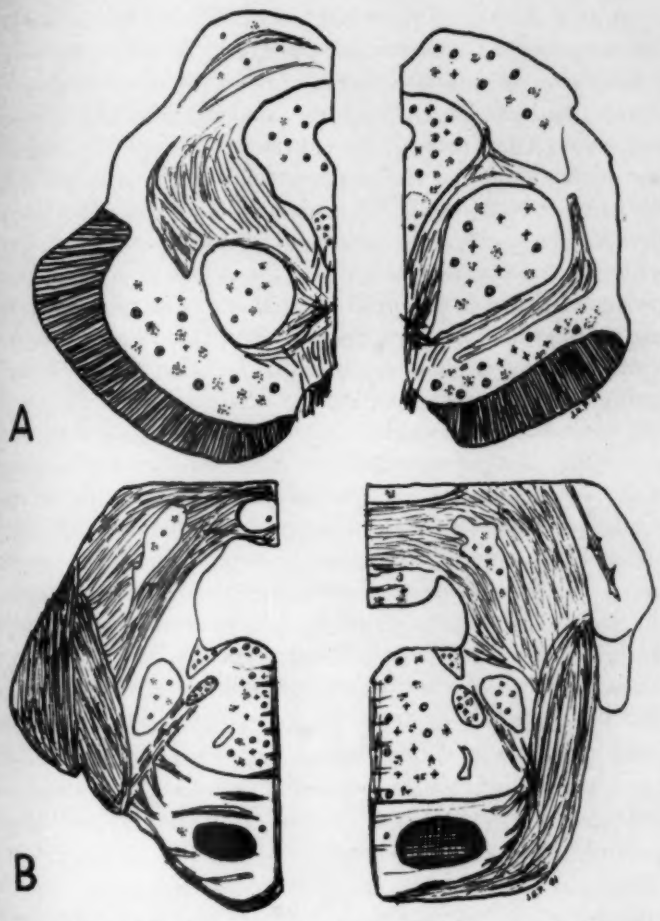

Fig. 2.—*A*, the midbrain at the level of the oculomotor nuclei; *B*, pons at the level of the roots of the fifth nerve.

but on the average the lesions in the monkey appeared to be the more destructive.

In the human brain stem a moderate degree of perivascular infiltration and focal microgliosis, but no necrotic cells, was noted in the anterior colliculi and periventricular gray matter. The inflammatory reaction

was a little more severe, and there were a few necrotic nerve cells in the oculomotor nuclei. The most intense inflammation appeared in the red nucleus and the substantia nigra. In the latter especially, occasional nerve cells were necrotic and were being phagocytosed, and a few recognizable leukocytes mingled with the reacting cells. No section of the medial geniculate body was available.

Lesions at this level in the monkeys examined showed rather wide irregular variation in severity from animal to animal. However, the mildest lesions in the monkey brain equaled in severity those in the human brain, and the majority of the animals presented considerably greater damage. A few necrotic nerve cells were frequently seen in addition to accumulations of inflammatory cells in the colliculi and periventricular gray matter, as well as in the oculomotor nuclei. The lesions in the red nucleus were more severe, often with necrosis of up to one-third of the large neurons. In spite of the presence of numerous dead cells, microglial reaction was relatively scanty, and frequently necrotic cells were seen without visible attempt at neuronophagia. The heaviest damage appeared in the substantia nigra. Thick collars of lymphoid cells surrounded the vessels, and there was marked focal and diffuse microglial proliferation. In some instances, the ground substance was loose and stringy and so crowded with phagocytic microglia as to form actual foam cell "abscesses." Necrosis varied from death of scattered cells to massive coagulation necrosis of the nerve cells of the whole central third of the substantia nigra. In such cases there was little or no attempt at neuronophagia. Such massive necrosis was apparently caused by direct action of the virus, as no evidence of vascular occlusion was seen. The medial geniculate body, seen in only a few animals, occasionally showed scanty perivascular round cell infiltration.

Pons.—Figure 2 *B* displays the general pattern of lesions in a section of the pons at the level of the roots of the fifth cranial nerve. In this region the lesions in the human brain and those in the average monkey brain were practically identical in their distribution, and they may conveniently be described together.

As shown in the diagram, the visible disease process was located predominantly in the tegmental portion of the pons. Lesions were constant and severe in the reticular substance, with necrosis of a number of cells, complete disappearance of some of the larger cells and an abundant cellular inflammatory reaction in the ground substance and the perivascular spaces. In both man and the average monkey, however, the most extreme damage in the reticular substance usually was seen caudal to this level in the midportion of the medulla.

The nuclei of the fifth cranial nerve showed quite marked inflammatory changes in man and in the majority of the monkeys. Only

scattered necrotic cells were seen. Generally these lesions, especially necrosis of neurons, were more pronounced in the motor nuclei of the fifth nerve. In a few monkeys necrosis and neuronophagia of single cells appeared among the large unipolar neurons of the mesencephalic root of the fifth nerve. These necrotic cells were usually found in the midbrain at the level of the colliculi. No damage to this structure was observed in the human brain.

In the locus caeruleus, as in the substantia nigra, a considerable degree of inflammation and cell necrosis was to be seen. The marked vulnerability of these groups of naturally pigmented neurons is a phenomenon for which no satisfactory explanation is at present available. It apparently cannot be attributed to peculiarities of their blood supply, or to their proximity to the ventricular lumen, and the neuronal connections of these two nuclear masses are still practically unknown. Generally, in the same animal lesions in the substantia nigra and locus caeruleus were of approximately the same degree of severity.

In contrast to the tegmentum, where the disease process was regularly severe, the interfascicular gray matter of the basal part of the pons seldom presented any visible damage. Occasionally there was some lymphoid infiltration about penetrating vessels, mostly in the median raphe, but this may well have been secondary to the inflammation in the tegmentum. Rarely there were one or two loose foci of microgliosis, but there was no evident necrosis in the interfascicular gray matter. A single focal lesion of this sort was seen in the human pons.

In both man and monkeys there was occasionally some neuroglial proliferation with probably slight demyelination immediately external to small vessels in the white matter. This lesion was most evident in the central white matter and peduncles of the cerebellum but was seen sparsely in the cerebral white matter.

Cerebellum.—Figure 3 *A* presents the general distribution of lesions in the cerebellar roof nuclei. For some reason the disease process in this region in the human brain was much less marked than that in the monkey brain. It was also less marked than that usually observed in brains from other human beings with poliomyelitis. In spite of this difference in severity, the lesions were practically identical as to pattern. The most severe damage regularly appeared in the tectal group of nuclei. Here there was considerable focal microgliosis, and usually there were scattered necrotic nerve cells. Lesions in the dentate nuclei were considerably less pronounced. Frequently there were a few large and rather dense nodules of microgliosis, between which the substance of the dentate nucleus showed no visible alteration. Only occasionally were a few necrotic nerve cells seen. Often the cerebellar cortex was apparently normal. In other animals there was scanty perivascular

infiltrations and small foci or vertical streaks of microgliosis in the molecular layer of the cortex. Such changes were almost always confined to the vermis. The selective localization of lesions of the cerebellum in these parts most directly connected with the vestibular nuclei was suggestive of an axonal route of dissemination of the virus. In

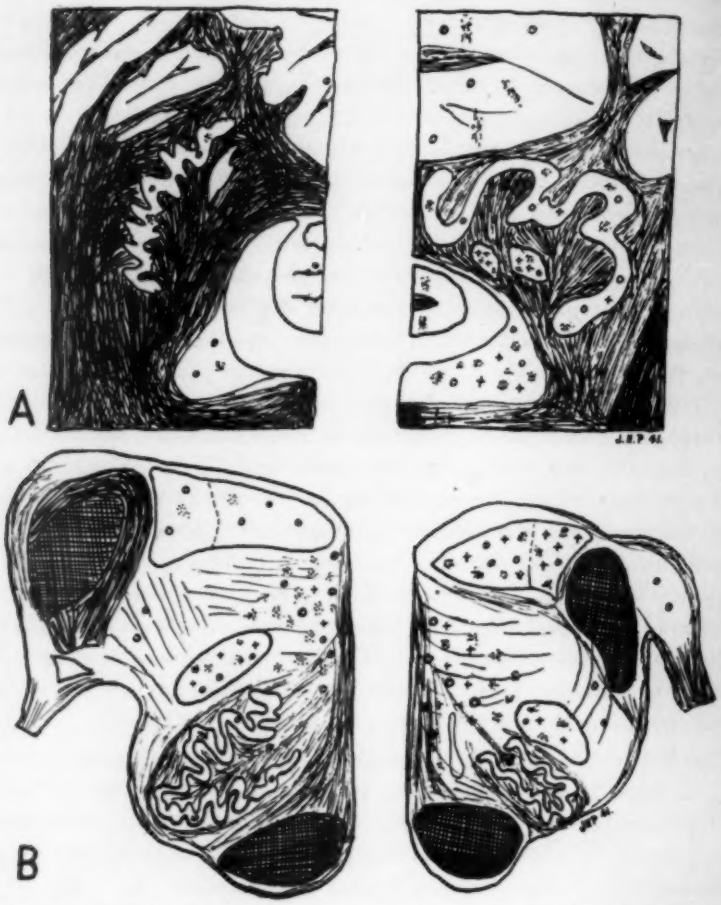

Fig. 3.—*A*, cerebellar roof nuclei; *B*, medulla at the level of the roots of the eighth nerve.

individual animals there was generally a rough agreement in severity between lesions in the vestibular nuclei in the affected portions of the cerebellum.

Medulla.—The distribution of the disease process in the medulla at the level of the eighth nerve roots is shown in figure 3 *B*. Except in the vestibular nuclei, the lesions in man and in the monkey were very

similar. In the reticular substance and in the caudal end of the facial nucleus there were a number of necrotic cells, marked focal and diffuse microgliosis and thick perivascular collars of lymphoid cells. In the spinal nucleus of the fifth nerve, only a few scanty perivascular infiltrations and, rarely, slight focal microgliosis were seen. As a rule, the gray matter of the inferior olives remained free of visible damage, though occasionally there were a few collars of lymphoid cells about vessels in the white matter of the hilus. In the human medulla and rarely in the monkey medulla single foci of microgliosis appeared in the olivary gray matter.

Rather unexpectedly, only moderate perivascular infiltration and a few microglial foci were present in the vestibular nuclei of the human medulla. In the brains of most of the monkeys and in other human brains the vestibular nuclei regularly showed severe damage. There was an intense cellular inflammatory reaction both in the form of perivascular collars and in that of focal and diffuse microglial proliferation. Necrosis of nerve cells was extensive, especially in the large cell lateral nucleus of Deiters, where in some specimens as many as half the cells were destroyed. In contrast to the vestibular nuclei, where severe damage was usually seen, the cochlear nuclei presented only occasionally a few scanty perivascular infiltrations.

No tissue from the human medulla caudal to the level of the eighth nerves was available for section. In the caudal portion of the monkey medulla the most severe lesions continued to be located in the reticular substance and less regularly in the nucleus ambiguus. Considerable cellular inflammatory reaction with more or less necrosis of neurons was seen in the nuclei cuneatus and gracilis in over two thirds of the monkeys. The hypoglossal nucleus suffered relatively little damage: in over two thirds of the animals no lesions were present; in the remainder the changes varied from minimal perivascular infiltration to occasionally marked unilateral damage with necrosis of cells. Lesions within the substance of the dorsal motor nucleus of the vagus were seen only once in this series of animals.

Spinal Cord.—Only a single section from a high cervical segment of the human cord was available for examination. Practically all the vessels in this section were surrounded by collars of lymphoid cells, but there was only scanty infiltration in the meninges. The anterior horns, especially their lateral parts, were heavily infiltrated with mononuclear inflammatory cells. Approximately two thirds of the nerve cells had disappeared. Of the remaining nerve cells, some were apparently normal, and others showed varying degrees of degeneration from chromatolysis to coagulation necrosis. The cellular inflammatory reaction had spread to some extent into the central gray matter and the posterior horns,

but definitely necrotic nerve cells were not present. There were also scattered small foci of cellular gliosis in the white matter.

Much of the cord tissue from monkeys was kept for virus, but the sections examined regularly showed a severe disease process in the cervical and lumbar enlargements. Possibly because the animals were usually killed as soon as paralysis became evident, coagulation necrosis of nerve cells was a more conspicuous feature than in the human cord, and complete loss of cells was less prominent.

SUMMARY

The topography of lesions in the brain from which the Lansing strain was originally isolated and in the brains of 23 rhesus monkeys used to isolate and propagate the virus from that brain have been described and illustrated.

The lesions in the human brain agreed in all essential details of type and distribution with those in a number of other brains from patients with poliomyelitis being studied in this laboratory. Generally the disease in the Lansing brain seemed anatomically rather less severe than that observed in other human specimens.

In distribution the lesions in the brains of the monkeys were closely analogous to those in the Lansing brain. No important or constant discrepancy appeared between man and monkeys in respect to structures damaged or structures spared in the brain.

In spite of the supposedly low susceptibility of monkeys, the disease in them was anatomically more severe than that in the human subject. The difference becomes even greater when it is recalled that all the animals were killed when paralysis was well established rather than after the disease had finished its natural course. The fact that the intracerebral route of inoculation was used may account for the marked lesions in the cortex and basal ganglions, but it does not so readily explain the extensive damage in the midbrain, cerebellum and medulla.

No evidence bearing on the possible routes of infection in the human subject was obtained in this study. The pattern of the fully developed disease was essentially identical in man and in the monkey though the route of inoculation was obviously different.

NERVES OF THE ADULT HUMAN ENDOMETRIUM

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A review [1] of the published reports emphasizes the limited information regarding the distribution of the intrinsic nerves in the human uterus. Although the cyclic physiologic activities of the adult human uterus are associated with vascular reactions, and vasomotor control through nerves is accepted without prejudice as regards other parts of the body, yet this correlation has not received consideration with uterine function because the fact of such nerve and blood vessel relations in the uterus never has been established and hormonal control has been emphasized. The rich innervation of the pelvic viscera, according to Bartelmez,[2] holds at least the anatomist against the view that the nerve fibers have no part in the uterine function. But, he added, there are no adequate studies of nerve endings in the ovary or uterus because no method can be relied on to demonstrate the finer fibers. Information concerning the intrinsic nerves of the endometrium therefore is meager. Stöhr [3] stated that nerves have been described in the mucosa of the uterus, even fine fibers to the epithelium, but the technic used by the authors of the reports was insufficient to establish the facts.

Kilian [4] (1852) was among the first to trace nerve fibers into the endometrium of the human uterus. Frankenhauser [5] described nonmyelinated fibers to the smooth muscle of the myometrium with branches to the stroma and the lining epithelium of the endometrium. Patenko,[6] Kostlin [7] and Clivio,[8] according to

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From the Henry Baird Favill Laboratory of St. Luke's Hospital and the Department of Pathology of the University of Chicago.

1. Brown, W. H., and Hirsch, E. F.: Am. J. Path., to be published.
2. Bartelmez, G. W.: Physiol. Rev. **17**:28, 1937.
3. Stöhr, P., in von Möllendorff, W.: Handbuch der mikroscopischen Anatomie des Menschen, Berlin, Julius Springer, 1928, vol. 4, pt. 1, p. 393.
4. Kilian, F. M.: Ztschr. f. rat. Med. **10**:41, 1851.
5. Frankenhauser, F.: Die Nerven der Gebärmutter und ihre Endigungen in der glatten Muskelfasern: Ein Beitrag zur Anatomie und Gynäkologie, Inaug. Dissert., Jena, Fr. Manke, 1867.
6. Patenko, T.: Zentralbl. f. Gynäk. **19**: 442, 1880.
7. Kostlin, R.: Fortschr. d. Med. **12**: 411, 1894.
8. Clivio, I.: Contributo alla conoscenza delle terminazioni nervose dell'utero, Pavia, tipog e legat. coop., 1894.

Dahl,[9] described a fine plexus of nonmedullated nerves in the "submucosa" from which fine fibrils extended to the epithelium of the endometrium. Von Gawronsky[10] demonstrated large nerve bundles extending parallel to the endometrial-myometrial junction, with fine branches into the endometrial stroma. Labhardt[11] and Mabuchi[12] were unable to find nerve elements in the endometrium. Dahl[9] described numerous fine nonmedulated nerve fibers in the endometrium, ending in small treelike branches in the stroma and as straight fibers between the cells of the epithelium. Davis[13] demonstrated nonmyelinated nerves beneath the epithelium of the cervix, but did not find nerve fibers beneath the mucosa of the body of the uterus. Brown and Hirsch[1] observed nerve fibers in the basal portions of the endometrium in the infantile uterus but were unable to establish the mode of termination in these immature tissues.

The confusion among observers regarding the presence of nerve fibers in the endometrium is due mainly to the inadequacy of the staining methods employed. The silver reduction methods used by most investigators do not clearly differentiate the nerves and reticulum fibers in the stroma of the endometrium. The blackening of the tissues conceals rather than differentiates the nerves from the other structures.

METHOD FOR DIFFERENTIATING NERVES FROM OTHER STRUCTURES OF HUMAN ENDOMETRIUM

The 4 adult uteri used in our study were obtained post mortem or by surgical extirpation from women 20 to 38 years of age. They had no obvious pathologic changes and were fixed promptly in Bouin's solution.[14] Penetration of the fixative into the tissues was facilitated by multiple needle injections of the solution. After twenty-four hours the uterus was bisected sagittally and each half bisected again longitudinally. Blocks of endometrium and adjacent myometrium about 1 cm. thick were cut and fixed further in Bouin's solution at ice box temperature for three to five days. The blocks at first were embedded in paraffin and then according to the double embedding method of the Bensleys.[15] The sections were cut serially at a thickness of 6 microns, mounted on slides and stained by Goldner's[16] modification of Masson's trichrome stain. Every third slide was stained routinely, and also series of consecutive slides were prepared. Several silver stains (Bielschowsky,

9. Dahl, W.: Ztschr. f. Geburtsh. u. Gynäk. **78**:539, 1916.

10. von Gawronsky, N.: Arch. f. Gynäk. **47**:271, 1894.

11. Labhardt, A.: Arch. f. Gynäk. **80**:135, 1906.

12. Mabuchi, K.: Mitt. a. d. med. Fak. d. k. Univ. Tokyo **31**:385, 1924.

13. Davis, A. A.: J. Obst. & Gynaec. Brit. Emp. **40**:481, 1933.

14. Saturated aqueous solution of trinitrophenol, 70 cc.; solution of formaldehyde 25 cc., and glacial acetic acid, 5.0 cc.

15. Bensley, R. R., and Bensley, S. H.: A Handbook of Histological and Cytological Technique, Chicago, University of Chicago Press, 1938, p. 56.

16. Goldner, J.: Am. J. Path. **14**:237, 1938.

Foley[17] and Bank and Davenport[18]) were used. Other uterine tissues were stained according to the technic of Spielmeyer[19] to distinguish myelinated and nonmyelinated fibers in the nerves.

OBSERVATIONS

With Goldner's modification of Masson's trichrome stain, the neurilemma sheaths of the nerves are pale green, the perineuriums and endoneuriums dark green and the Schwann cells and the perineurial and endoneurial nuclei purple-red. The axis-cylinders, recognized with difficulty, are pale red. The nerves contrast sharply against the dark green compact collagenous connective tissues, the brick red smooth muscle fibers of the myometrium and blood vessels and the dark red nuclei and reticular fibers of the endometrial stroma. Large nerves are demonstrated more clearly by the Goldner modification of Masson's trichrome stain than by the silver reduction methods. The silver stains do not differentiate the ultimate twigs of the fine terminal axons of the nerves from the reticulum fibers of the endometrial stroma.

Large nerves enter the uterus in the region of the cervix and along the lateral side of the corpus at the level of attachment of the broad ligaments. They pass into the deeper portions of the myometrium, ascend parallel to the cavum of the uterus and finally enter the endometrium (fig. 2 *A*). In the inner fourth of the myometrium the nerves extend for some distance along the large vessels. Branches or the main trunks of nerves leave the vessels and course through the myometrium to join with other blood vessels at different levels.

The main nerve trunks or their large branches approach the spiral arteries at their points of bifurcation in the inner fourth of the myometrium. Here branches of the nerves and the adventitia of the arteries seem to merge (fig. 5 *B*).

At various levels branches arise from the large nerves in the inner fourth of the myometrium and accompany the spiral or the basal arteries through tissue crevices into the endometrium (fig. 2 *A*). In the basal portions of the endometrium some of the nerves branch dichotomously, each division extending parallel to the myometrial edge (fig. 2 *B*). Others on entering the endometrium do not divide but bend sharply and pass along the endometrial-myometrial junction (fig. 2 *A*). These primary divisions are large (130 microns; fig. 1 *A* and *B*) and long. They may extend toward the fundus, toward the cervix or transversely around the uterus. Throughout their course they give off secondary branches (fig. 3 *A*) to the basal arteries. One primary division of the endometrial nerve thus supplies many arteries. The nerves approach the basal arteries at the endometrial-myometrial junction (figs. 3 *B*, 4 *A* and *B* and 5 A) or in the immediately underlying myometrium at the bifurcation of these vessels (figs. 1 *B* and 3 *B*). The exact and ultimate mode of termination of the nerves along the arteries was not determined, because the axis-cylinders do not stain distinctly and after their sheaths are lost are not differentiated clearly from the other histologic elements of the arterial wall. Other branches of the endometrial nerves appear to end in the stroma (fig. 3 *A*); whether free or in relation to capillaries

17. Foley, J. O.: Stain Technol. **13**: 5, 1938.

18. Bank, E. W., and Davenport, H. A.: Stain Technol. **15**:9, 1940.

19. Spielmeyer, W., in Mallory, F. B.: Pathological Technique, Philadelphia, W. B. Saunders Company, 1938, p. 237.

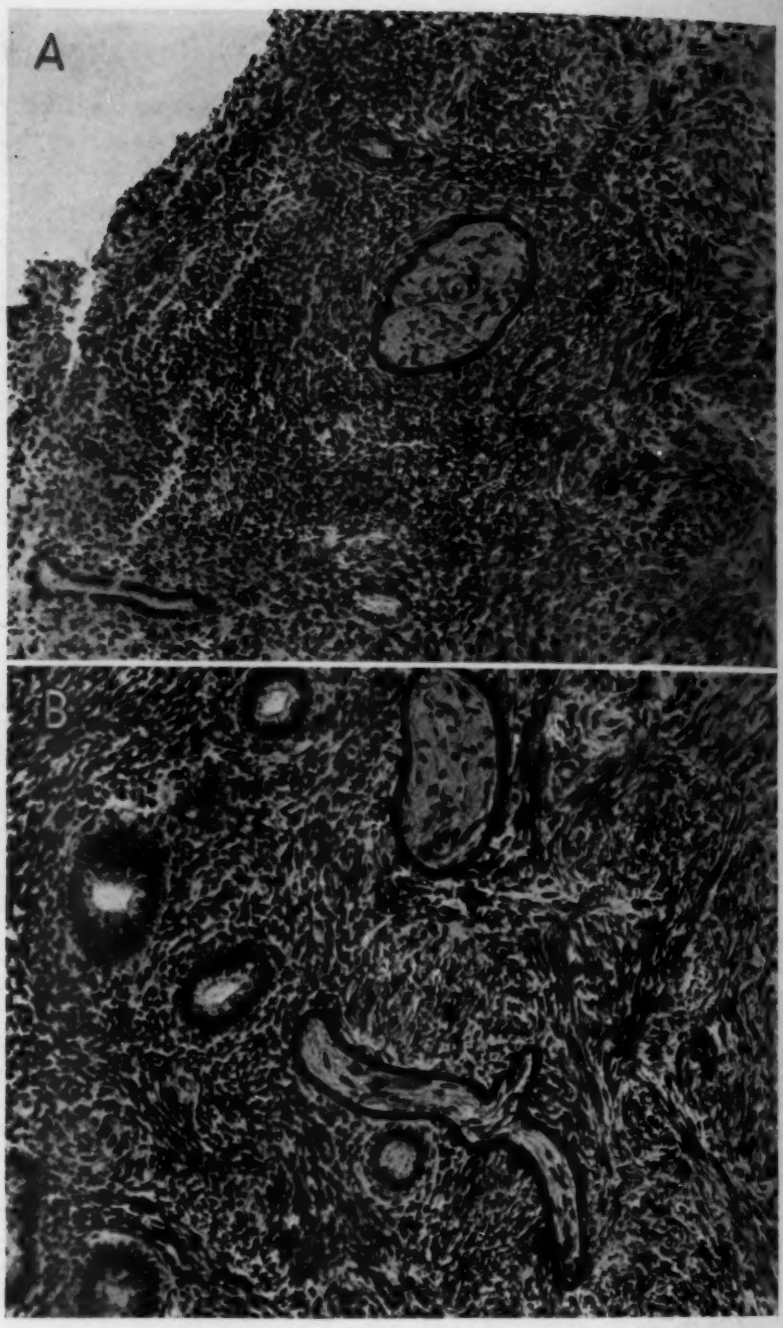

Fig. 1.—*A*, photomicrograph illustrating a large nerve trunk with a nutrient artery in the basal portion of the endometrium. × 198. *B*, photomicrograph illustrating a large nerve trunk separated into bundles in the basal portion of the endometrium. In the lower half a branch from this nerve trunk curves into a crevice of the myometrium. × 198.

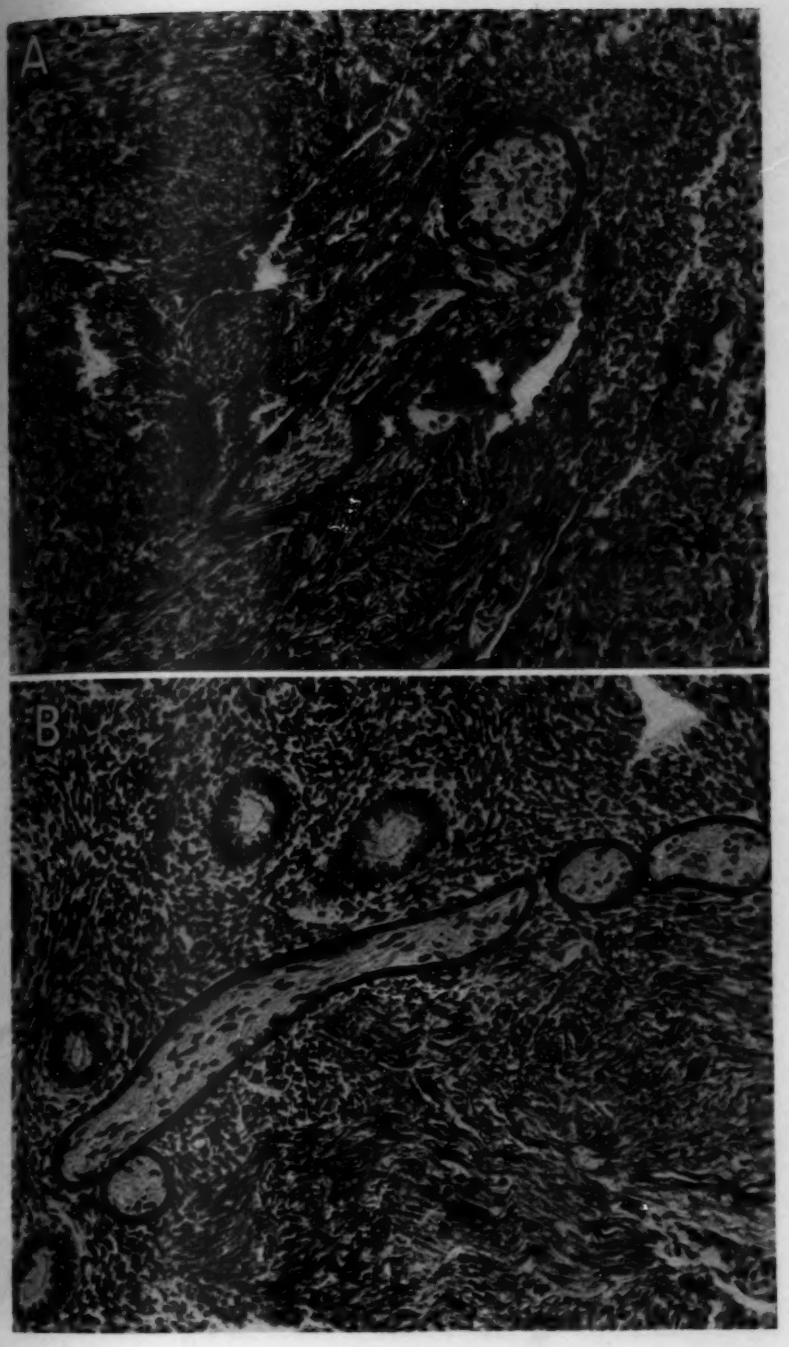

Fig. 2.—*A*, photomicrograph illustrating a nerve trunk that approaches the endometrium through a tissue crevice and, after curving sharply, extends along the endometrial-myometrial junction. × 198. *B*, photomicrograph illustrating a longitudinal section through a nerve trunk in the basal portion of the endometrium. × 198.

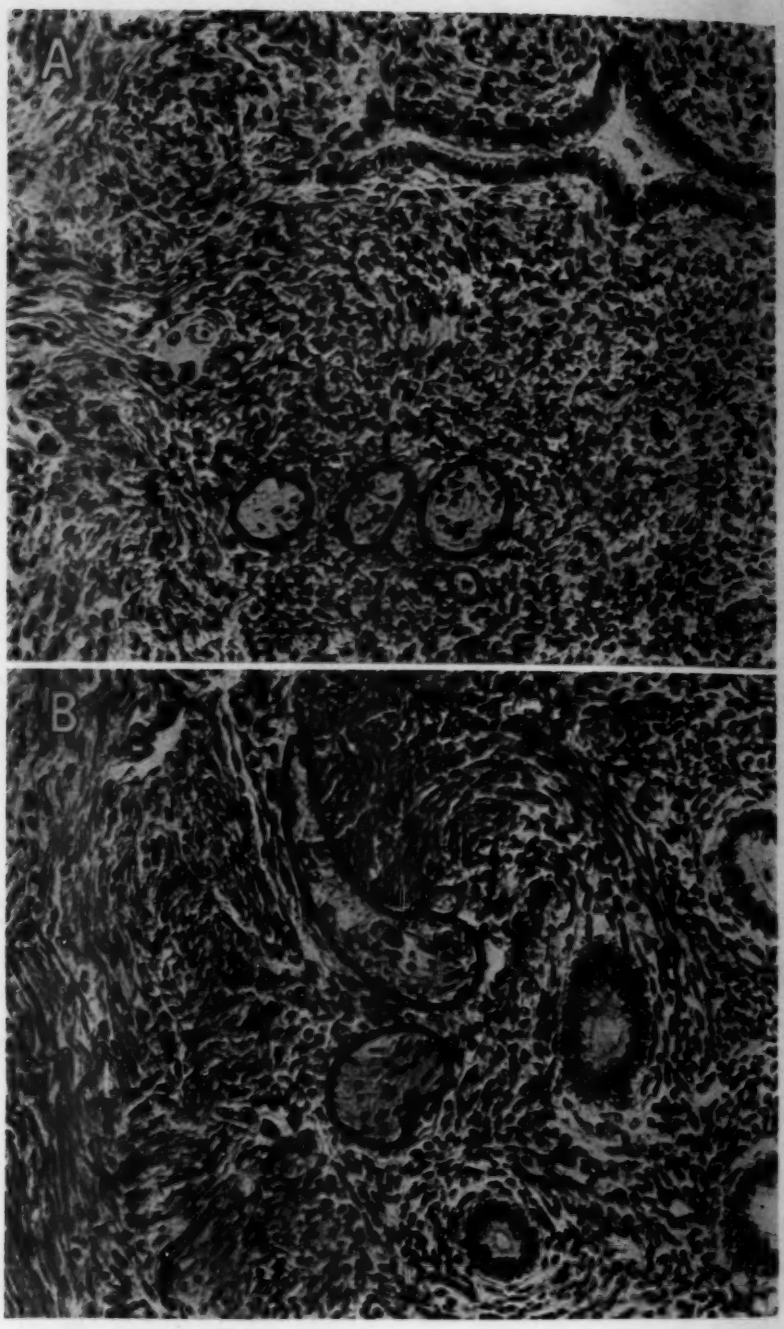

Fig. 3.—*A*, photomicrograph illustrating three branches of a large nerve in the endometrium. The one in the center is divided into two bundles. Below the right branch is a small fiber that was traced through a series of sections and seemed to end in the stroma. × 270. *B*, photomicrograph illustrating a nerve below a basal artery. Immediately above the basal artery is a small branch from the main nerve. × 270.

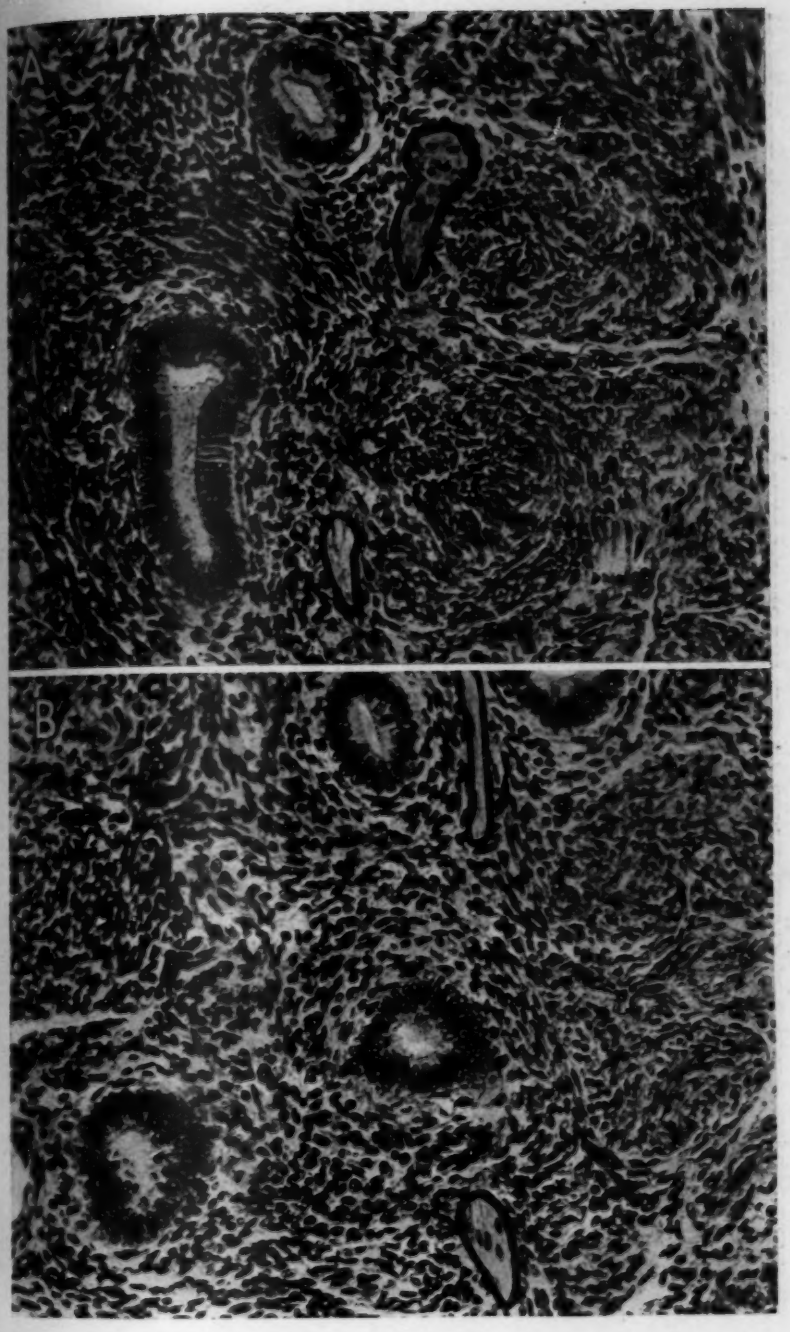

Fig. 4.—*A*, photomicrograph illustrating two short segments of a nerve fiber in the endometrium, approaching and ending above in a basal artery. × 270. *B*, photomicrograph illustrating short segments of two nerve fibers in the endometrium, the upper segment coming down to a basal artery. × 270.

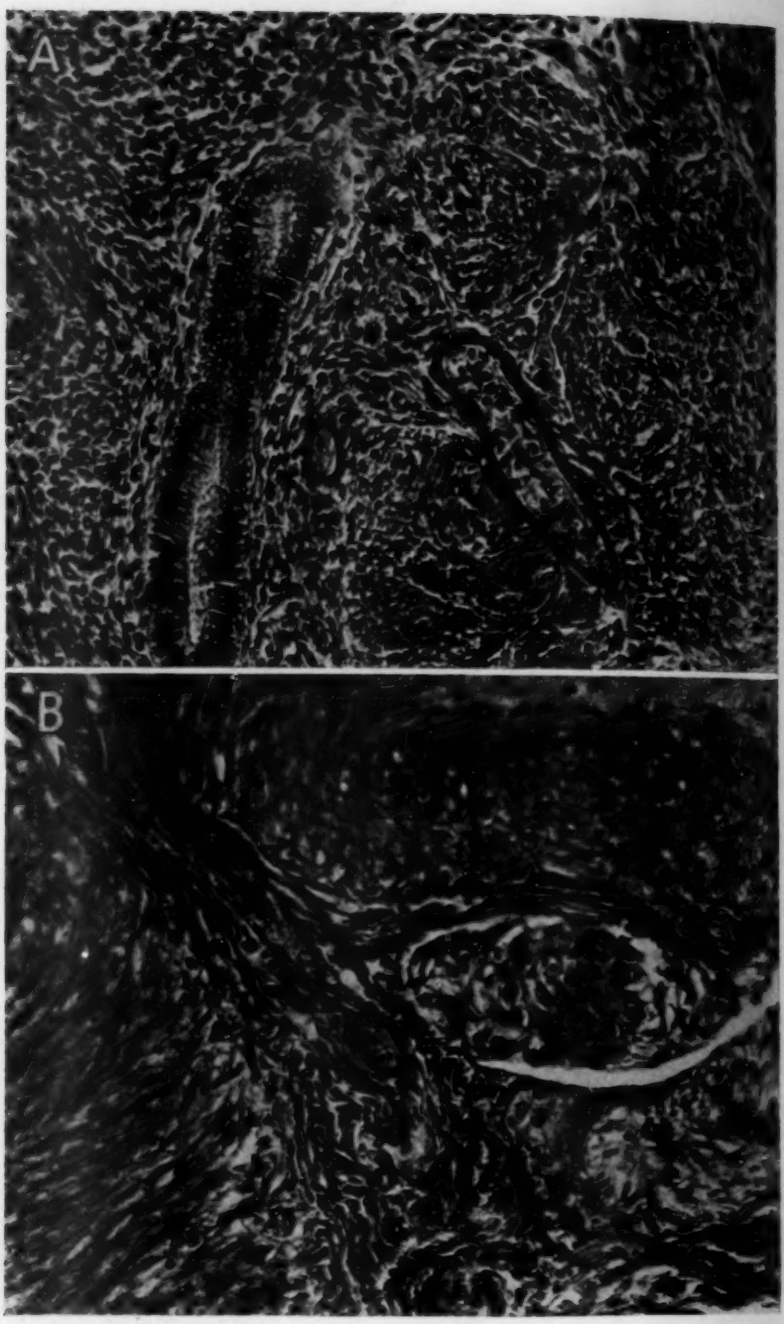

Fig. 5.—*A*, photomicrograph illustrating a nerve fiber in the endometrium about to join a basal artery entering from the myometrium. × 270. *B*, photomicrograph illustrating a nerve fiber in the adventitia of one of two spiral arteries after their bifurcation from a main artery in the inner fourth of the myometrium. × 270.

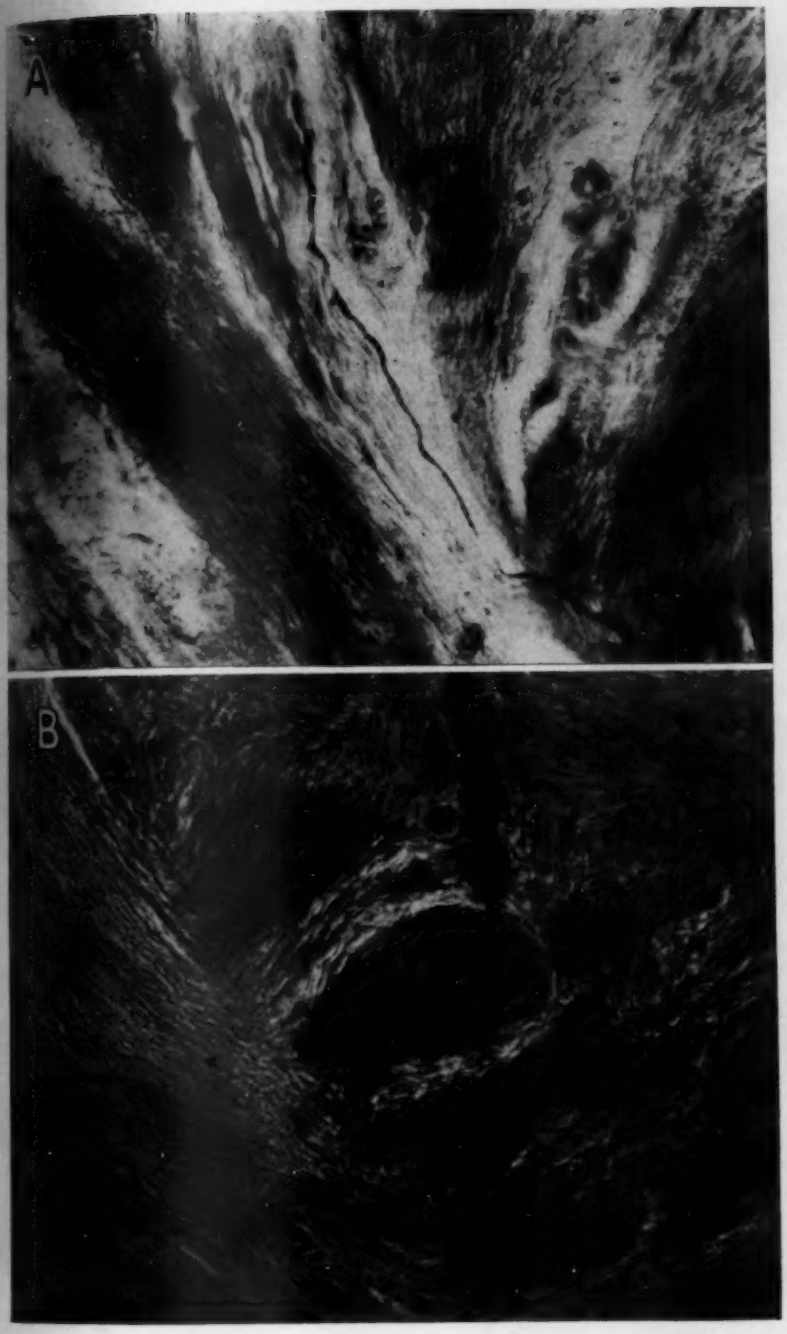

Fig. 6.—*A*, photomicrograph illustrating a nerve with a long myelinated fiber. × 270. *B*, photomicrograph illustrating an oblique section of a nerve with several myelinated nerve fibers. × 270.

was not established. After giving off multiple secondary branches, the primary divisions of the endometrial nerves also end in relation to the basal arteries or in the stroma. Nerves were not found beyond the basal third of the endometrium, nor did any nerve fibers extend to the epithelium of the deeper portions of the uterine glands. Nutrient arteries are numerous in the large nerves of the myometrium and endometrium. They extend only a short distance within the nerves (fig. 1 *A*). In endometrial and myometrial tissues stained by the Spielmeyer method the nerve trunks (fig. 6) in the muscle and those approaching the endometrium consisted mainly of nonmyelinated fibers. One or several nerve fibers with myelinated sheaths, however, were in these nerve trunks. No neuroganglions or neurons were demonstrated in the endometrium.

COMMENT

In man and monkeys the endometrium, according to Daron,[20] Bartelmez [21] and Jones and Brewer,[22] has a double arterial blood supply: (1) long coiled spiral arteries, which supply the superficial two thirds, and (2) straight or basal arteries, which supply the basal one third of the endometrium. Before and during menstruation these two sets of arteries behave differently. The spiral arteries are constricted; the basal arteries remain dilated. Not all spiral arteries constrict simultaneously, and the regions of constriction are limited to the inner fourth of the myometrium and basal portions of the endometrium. Hormonal or endometrial degradation products causing this localized selectivity of vasoconstriction have been emphasized by Markee,[23a] with exclusion of a nervous mechanism of control. The spiral and basal arteries, having different nerve supplies, may act independently or synchronously. Other experimental observations favor nerve control of the endometrial arteries. In the rabbit's uterus, Markee [23b] observed rhythmic waves of vasoconstriction and vasodilatation passing from the horns to the cervix. After a small localized region of the uterus was painted with nicotine, waves of vasoconstriction occurred proximal but not distal to the region of application. This indicates nerve control of the vascular rhythmicity as well as the presence of synapses in the controlling nerve pathway, because nicotine prevents the transmission of nerve impulses only at the synaptic junctions (Sollmann [24]). Markee [23a] observed rhythmic vascular changes also in intraocular endometrial transplants in rabbits and monkeys. Just prior to menstruation in the monkey and the human

20. Daron, G. H.: Am. J. Anat. **58**:349, 1936.

21. Bartelmez, G. W.: Am. J. Obst. & Gynec. **21**:623, 1931; Contrib. Embryol. (no. 142) **24**:141, 1933; J. A. M. A. **116**:702, 1941.

22. Jones, H. O., and Brewer, J. I.: Am. J. Obst. & Gynec. **38**:839, 1939.

23. Markee, J. E.: (*a*) Contrib. Embryol. (no. 177) **28**:219, 1940; (*b*) Am. J. Physiol. **100**:374, 1932.

24. Sollmann, T.: A Manual of Pharmacology, ed. 5, Philadelphia, W. B. Saunders Company, 1939, p. 389.

species the periods of vasoconstriction in the uterus are lengthened sufficiently, according to Bartelmez,[21] to produce ischemic necrosis of the endometrium with subsequent menstrual bleeding.

Occasionally, transection of the spinal cord induces menstrual bleeding. Disturbances of the vasomotor control of the blood vessels of many organs whose nerves arise below the level of transection follow such a lesion (Best and Taylor [25]). The assumption that a similar loss of vasomotor control of the endometrial arteries leads to prolonged vascular congestion and induced menstruation after injury of the spinal cord seems logical.[26] The vasomotor nerve regulation of the blood vessels in other tissues of the body suggests a similar influence on the endometrial blood vessels.

Markee's [23] observations on intraocular endometrial transplants in rabbits and monkeys seem to deny the possibility of nerve regulation of the endometrial blood vessels. Little is known about the nerve supply of the endometrium in these animals, but since nerves are present in the endometrium of the human uterus, their functional significance cannot be disregarded. Markee's statement that constriction of the spiral arteries is due to compression of their walls secondary to the rapid regression of the endometrium preceding the menstrual bleeding has several objections: (1) The myometrial as well as the endometrial portions of the spiral arteries are contracted; (2) not all spiral arteries are contracted simultaneously in a given region of regression; (3) the arteries do not remain continuously constricted but have short periods of relaxation alternating with the periods of contraction, and (4) during regression of the endometrium the basal arteries remain dilated although the pressure on the two sets of vessels is the same and the basal arteries are smaller and have thinner walls than the spiral arteries.

The stains for myelinated nerves demonstrated that most of the fibers in the nerve trunks are without medullary sheaths. Accordingly, these nonmyelinated fibers have the characteristics of vasomotor nerves elsewhere in the body,[27] are postganglionic and probably belong to the sympathetic nervous system. The few myelinated fibers in the nerve trunks have the anatomic structure of sensory nerves.

Nerves are found only in the basal third of the endometrium, which under normal conditions remains intact during menstruation. Thus located, the endometrial nerves do not desquamate and regenerate with each menstrual cycle.

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25. Best, C. H., and Taylor, N. B.: The Physiological Basis of Medical Practice, ed. 2, Baltimore, Williams & Wilkins Company, 1939, p. 404.

26. Markee, J. E.; Davis, J. H., and Hinsey, J. C.: Anat. Rec. **64**:231, 1936.

27. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929, p. 140.

SUMMARY

Goldner's modification of Masson's trichrome stain is an excellent differential stain for demonstrating nerves in the endometrium. It offers many advantages over silver stains but does not contrast the axis-cylinders sufficiently to demonstrate the ultimate terminations of the nerve fibrils.

Large nerve trunks and their branches are distributed in the basal third of the endometrium. The terminal branches of the endometrial nerves extend to the basal arteries; some seem to end freely in the stroma of the endometrium. The large nerve trunks in the myometrium and those approaching the endometrium contain mainly nonmyelinated fibers. A few fibers are myelinated. Accordingly, the nonmyelinated components agree in structure with vasomotor nerves elsewhere in the body, are postganglionic and probably belong to the sympathetic nervous system. The myelinated fibers have the anatomic structure of sensory nerves.

The distribution of the nerve supply of the spiral and that of the basal arteries of the endometrium apparently are distinct. The spiral arteries are innervated in the inner fourth of the myometrium near their bifurcation; the basal arteries are supplied by nerves in the basilar portions of the endometrium or in the immediately underlying myometrium.

A vasomotor nervous mechanism in the control of the vascular reactions of the endometrial arteries during the menstrual cycle is suggested by this anatomic study.

RELATION OF NEPHROSIS AND OTHER DISEASES OF ALBINO RATS TO AGE AND TO MODIFICATIONS OF DIET

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In few experiments dealing with the relation of diet to the life span has emphasis been placed on the spontaneous diseases peculiar to the species. Several naturally occurring diseases are found so frequently in albino rats of advanced age that they may be considered as factors limiting the average life span. It is therefore of importance to determine if the development of these conditions is influenced by diet.

This report is based on postmortem examinations of 216 rats which were used in an experiment designed to study the nutritional requirements of the latter half of the rat's life. The details of the procedures and the statistical analyses of longevity and of organ weights have been reported by McCay and associates.[1] The purposes of the present report are to describe the diseases most commonly observed and to show their relation to age and to the diets used in this experiment.

MATERIAL AND METHODS

A total of 329 male albino rats of the Yale (Osborne-Mendel) strain, ranging from 200 to 450 days of age, were divided into sixteen groups of 20 or 21 animals on the basis of the following four pairs of variables: high and low protein, milk protein and liver as the source of protein, exercise and no exercise, and unrestricted and moderately restricted diet. The rats were equally distributed among the groups with respect to age. The regimens for each of the sixteen groups are shown in table 1.

Previous to the start of the experiment all rats were fed the stock diet of calf meal,[2] which was 19 per cent digestible protein. The percentages of the main constituents of the four basal diets are shown in table 2. The term "casein" is

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1. McCay, C. M.; Maynard, L. A.; Sperling, G., and Osgood, H. S.: J. Nutrition **21**:45, 1941.

2. Maynard, L. A.: Science **71**:192, 1930.

used to designate groups receiving diets in which the main source of protein was a mixture of casein and lactalbumin. All groups received the same amount of the basal diets, but the unrestricted groups were given a supplement of fat and carbohydrate in unlimited amount. By adjustment of the daily ration of each basal diet, rats receiving this ration alone were maintained at 90 per cent of the weight of those receiving the supplement. Exercise was given by means of a rotating cylindric cage.

Most of the rats were kept on the regimens until they died; but 4 rats from each of the sixteen groups were killed for examination during the course of the experiment. These animals were selected on the basis of healthy appearance in

TABLE 1.—*Regimens of the Sixteen Experimental Groups*

Group 1.	High protein—casein—exercise—restricted diet
Group 2.	High protein—casein—exercise—unrestricted diet
Group 3.	High protein—casein—no exercise—restricted diet
Group 4.	High protein—casein—no exercise—unrestricted diet
Group 5.	High protein—liver—exercise—restricted diet
Group 6.	High protein—liver—exercise—unrestricted diet
Group 7.	High protein—liver—no exercise—restricted diet
Group 8.	High protein—liver—no exercise—unrestricted diet
Group 9.	Low protein—casein—exercise—restricted diet
Group 10.	Low protein—casein—exercise—unrestricted diet
Group 11.	Low protein—casein—no exercise—restricted diet
Group 12.	Low protein—casein—no exercise—unrestricted diet
Group 13.	Low protein—liver—exercise—restricted diet
Group 14.	Low protein—liver—exercise—unrestricted diet
Group 15.	Low protein—liver—no exercise—restricted diet
Group 16.	Low protein—liver—no exercise—unrestricted diet

TABLE 2.—*Percentage Composition of the Basal Diets*

	High Protein		Low Protein	
	Casein	Liver	Casein	Liver
Cooked starch	34	34	65	65
Casein	20	..	4	..
Lactalbumin	4	..	3	..
Sucrose	10	10	10	10
Cellulose	2	2	2	2
Butter	5	5	5	5
Lard	7	..	2	..
Yeast (irradiated)	5	5	5	5
Salt mixture	4	3	4	3
Dry liver	..	41	..	10

an effort to separate the changes due to age alone and to the effects of the diets from the effects of intercurrent diseases. All of the rats selected for examination had been from 200 to 300 days of age when placed on the diets and ranged from 259 to 620 days of age when killed.

Routine pathologic examinations of the rats dying of natural causes were not made until nearly one half of the rats in the experiment had died. For this reason the pathologic study for the most part represents a cross section of rats already in advanced age. The age distribution of rats that died and the proportion examined are shown in table 3. Of the 265 rats that died, 152 (57 per cent) were examined. The youngest rat examined was 428 days of age, and the oldest was 1,135 days old. There were 5 rats less than 500 days of age and 5 rats over 900 days old. Tissues for microscopic examination were fixed in Bouin's solution, embedded in paraffin and stained with hematoxylin and eosin.

RESULTS

The pathologic conditions most frequently found in the 216 rats examined were: chronic pneumonia or bronchiectasis, chronic nephrosis and tumors of various types. These conditions are described in the following pages, and their frequency is tabulated both with respect to age and with respect to each of the variables of the experiment. To judge the effects of any single pair of variables, it was possible to combine all of the groups into two large groups. For example, as shown in table 1, all rats on the high protein diets could be compared with all on the low protein diets. This method of analysis has been used with every pair of variables in relation to the frequency of each disease. Because of differences in age, selection and manner of death, the frequency of disease in the killed rats is tabulated separately from that in rats dying of natural causes. Where both are combined in the tables, the mode of death is indicated.

TABLE 3.—*Age Distribution of Rats That Died and Proportion Examined*

Age in Days	Rats That Died	Rats Examined	Percentage Examined
Up to 500	124	32	25.8
600 to 699	66	45	68.2
700 to 799	51	51	100.0
Over 800	24	24	100.0
Total	265	152	57.3

Chronic Pneumonia (Bronchiectasis).—Chronic pneumonia (bronchiectasis) was the pathologic condition most frequently encountered, being present in 81 per cent of rats dying naturally and in 37 per cent of those killed. The condition has long been recognized as a common disease of rats and has been described by Hektoen,[3] Tunnicliff,[4] Nelson and Gowen,[5] Moise and Smith,[6] Klieneberger and Steabben[7] and many others. Among the descriptive names that have been suggested are: "bronchopneumonia," "bronchiectasis," "chronic pneumonia" and "pulmonary abscess." In its various stages the disease may show any of these features. The cause remains obscure despite studies in many laboratories. Various organisms have been cultured from affected lungs, but no one organism appears to have been found consistently. The evidence obtained by Klieneberger and Steabben points to Strepto-

3. Hektoen, L.: Tr. Chicago Path. Soc. **10**:105, 1916.

4. Tunnicliff, R.: J. Infect. Dis. **19**:767, 1916.

5. Nelson, J. B., and Gowen, J. W.: J. Infect. Dis. **46**:53, 1930. Nelson, J. B.: ibid. **46**:64, 1930.

6. Moise, T. S., and Smith, A. H.: Arch. Int. Med. **45**:92, 1930.

7. Klieneberger, E., and Steabben, D. B.: J. Hyg. **37**:143, 1937.

bacillus moniliformis together with certain micro-organisms like those of pleuropneumonia of cattle as being the etiologic agents. However, their pathogenicity for the rat has not been established.

The disease was encountered in all degrees of severity in this series, varying from local dilatation of bronchioles to extensive abscess formation and pulmonary fibrosis. As Klieneberger and Steabben have pointed out, the earlier stages of the disease appear to be characterized or accompanied by a great increase in peribronchial lymphoid tissue, which forms thick sheaths about the main bronchi and bronchial branches and often extends into the submucosa. In our series this submucosal infiltration was most conspicuous in lungs showing early stages of the disease. The suggestion is offered that the massive infiltration of lymphoid tissue into the submucosa may favor mechanical obstruction of the passages and thus be an important factor in the development of bronchiectasis.

Tables 4 to 6 show the frequency of chronic pneumonia with respect to age and to the experimental regimens. It will be seen from table 4 that there is a definite increase in frequency of the condition in the younger groups with advance in age (from 200 to 620 days). In rats of comparable ages there is a greater frequency in those that died than in those that were killed. This suggests that chronic pneumonia is an important factor in bringing about the deaths of animals of this age range. After 600 days there is no change in the frequency with age. This fixed frequency may occur because these animals are all relatively old rats or because they are in a sense a selected group, the less hardy animals of the experiment having succumbed at an earlier age. It will be noted from tables 5 and 6 that the frequency of pulmonary disease has not varied with the experimental regimens, and this uniformity makes comparison with other lesions which vary under the same conditions more significant.

Chronic Nephrosis.—A characteristic lesion, here designated as chronic nephrosis, was found in the kidneys of 44 per cent of rats dying naturally and in 14 per cent of those killed. The microscopic picture was similar to that described by Moore and Hitchcock [8] and by Wilens and Sproul.[9] This lesion has often been observed in older rats of this colony maintained on the stock diet of calf meal (figure). It has also been observed in old rats used in other experiments. In all experimental groups of this series, in stock animals and in animals receiving other experimental diets, the lesion increases with age and hence is perhaps a factor in determining the life span. It is therefore not considered

8. Moore, R. A., and Hitchcock, F. A.: Proc. Soc. Exper. Biol. & Med. **27**:706, 1930.

9. Wilens, S. L., and Sproul, E. E.: Am. J. Path. **14**:201, 1938.

as a disease produced specifically by the diets of this experiment but as a common spontaneous disease of the albino rat.

The affected kidneys were occasionally enlarged, were usually yellow-brown and presented finely irregular surfaces. Always both kid-

TABLE 4.—*Frequency of Bronchiectasis with Respect to Age*

Age in Days	Rats Examined	Rats with Bronchiectasis	Frequency of Bronchiectasis
Rats killed			
200 to 299	14	0	0
300 to 399	30	13	43.3%
500 to 620	15	9	60.0%
Rats that died			
Up to 599	27	23	85.2%
600 to 699	40	33	82.5%
700 to 799	48	38	79.2%
Over 800	23	18	78.3%

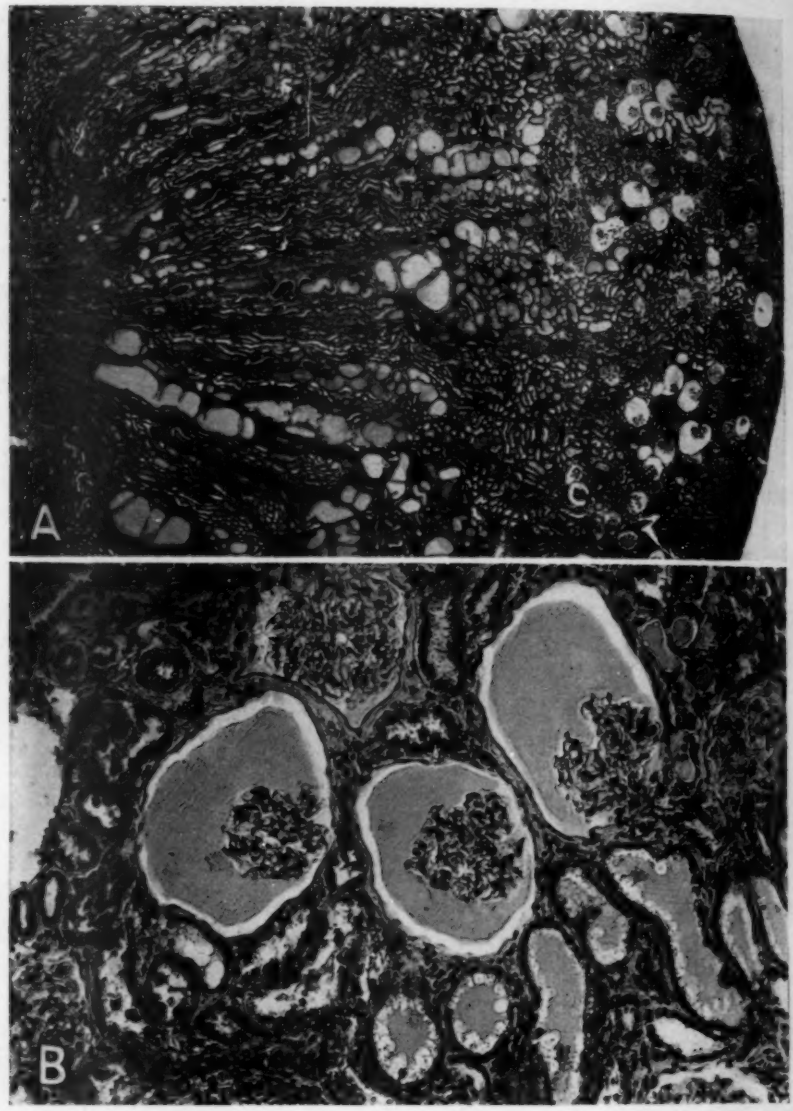
TABLE 5.—*Frequency of Bronchiectasis with Respect to the Experimental Groups Among Rats Killed*

Experimental Group	Rats Examined	Rats with Bronchiectasis	Frequency of Bronchiectasis
High protein	30	12	40.0%
Low protein	29	10	34.5%
Casein	30	9	30.0%
Liver	29	13	44.8%
Exercise	29	12	41.4%
No exercise	30	10	33.3%
Unrestricted diet	29	8	27.6%
Restricted diet	30	14	46.6%

TABLE 6.—*Frequency of Bronchiectasis with Respect to the Experimental Groups Among Rats That Died*

Experimental Group	Rats Examined	Rats with Bronchiectasis	Frequency of Bronchiectasis
High protein	67	52	77.6%
Low protein	71	60	84.5%
Casein	62	48	77.4%
Liver	76	64	84.2%
Exercise	72	58	80.5%
No exercise	66	54	81.8%
Unrestricted diet	64	54	84.4%
Restricted diet	74	58	78.4%

neys were involved. The essential microscopic changes were the presence of large hyaline casts in tubules of the cortex and medulla, dilatation of adjacent glomerular capsules, hyaline thickening of the basement membranes of affected renal units and increase in fibrous tissue about these units. The number of renal units exhibiting these changes varied in different kidneys, and even in the kidneys showing the most advanced examples many relatively normal glomeruli and tubules were seen.



A, low power view of a section of a kidney from a rat, showing occlusion of tubules of the medulla and aglomerular zone of the cortex by albuminous casts, with dilatation of glomerular spaces. This rat was killed at 500 days of age and had received a stock diet of calf meal. × 18. *B*, high power view of an area of the cortex of the kidney shown in *A*. Note the casts in convoluted tubules, the dilatation of glomerular spaces and the slight thickening of the basement membranes of the glomerular capsules. × 150.

From a study of kidneys showing different degrees of damage, it was possible to trace the development of the lesions. In the least affected kidneys, a few small casts were seen in collecting tubules, but no changes were evident in the glomeruli or the convoluted tubules. With more extensive involvement, groups of hyaline casts of various sizes were seen in tubules of the medulla, and hyaline casts appeared in convoluted tubules of the cortex. The glomerular capsules of affected renal units were moderately or extensively dilated and often contained a small amount of coagulated material within the capsular spaces. Associated with the distention of tubules by hyaline material there was moderate compression of the tubular epithelium. Atrophy of the epithelium occurred in tubules which contained very large casts. In the cases in which the changes were most advanced, there was progressive involvement of larger numbers of renal units, and thickening of basement membranes became conspicuous. There was an increase in fibrous tissue as well as slight lymphocytic infiltration about the involved tubules and glomeruli. Many glomerular tufts appeared to undergo fibrous atrophy, but the glomerular spaces were not obliterated. Vascular changes were rare and usually of slight degree, and were not seen in association with the early or the moderately advanced lesions. There was no evidence of glomerulitis or of pyelonephritis.

In an attempt to clarify the genesis of these changes, renal function was studied. The urine and blood of the rats in this experiment were not examined, but determinations carried out on the blood and urine of animals of the same age and strain showed that most of the rats over 300 days of age excreted albumin in large amounts. Many of these rats were found to have renal lesions similar to those described. The excretion of phenolsulfonphthalein by these animals was usually within normal limits, and the level of the blood urea nitrogen was not elevated. A supplementary experiment, carried out with the assistance of Dr. G. H. Ellis, indicated that the amount of protein excreted on a high liver diet was greater than that on a low liver diet.

From the morphologic and functional evidence, therefore, it appears possible that the disease is a progressive degeneration initiated and perhaps maintained by excretion of large amounts of urinary protein. It seems probable that under a condition of high excretion of protein casts may form, first in the collecting tubules, thus producing partial obstruction of nephrons. This process may favor further formation of casts and dilatation of the more proximal parts of the renal units. Fibrosis may then occur about the damaged units. An analogous lesion is the nephrosis associated with Bence Jones proteinuria, in which the convoluted tubules became occluded by casts of the associated protein. The protein of rat urine does not, however, have the character of Bence Jones pro-

tein. From the data available it appears justifiable to regard the condition as chronic nephrosis following obstruction of tubules.

Tables 7 to 10 show the frequency of chronic nephrosis with respect to age and the variables of the experiment. Further analyses are shown in tables 11 to 12. Table 7 shows that there is an increase in frequency of chronic nephrosis with advance in age. It is possible that the slightly lower frequency in rats over 800 days of age is related to the relatively small number of animals on the high casein unrestricted regimen which lived to this age. All of the 13 animals on the high casein unrestricted diet showed evidence of the disease, and all but a single rat died before the age of 800 days (table 12). McCay and associates [1] have shown that this diet shortened significantly the mean life span as compared with other diets of this experiment. It is apparent from tables 8 and 9 that exercise was not an important factor in the production of the disease and that the condition was slightly more common in rats with no enforced exercise. However, in both the rats killed and those that died a high protein level, casein and an unrestricted diet appeared to favor the development of chronic nephrosis. These factors are analyzed further in tables 11 and 12, in which it is seen that the effect of the regimens named is cumulative. Of the three variables considered in these tables, the unrestricted diet seemed to exert the most pronounced effect. In the killed rats there was increased frequency of the chronic nephrosis with increasing age in all of the experimental groups, as shown in table 10. The same relation to age was found in the rats that died but was less clearly defined owing to the early death of many animals on the high casein unrestricted regimen.

Tumors.—A total of 51 tumors was found in 48 of the 216 rats examined, including those killed and those that died naturally, a frequency of 22.3 per cent. The occurrence of these tumors is analyzed in tables 13 to 15. The majority of the tumors were diagnosed as lymphosarcoma. These usually developed in the lungs or adjacent tissue and occasionally metastasized to distant organs. They resembled in all respects the lymphoid tumors described by Bullock and Curtis [10] and by Nelson and Morris.[11] The next largest group of tumors was derived from connective tissue. They frequently arose subcutaneously and occasionally showed evidence of malignancy. There were two epithelial tumors; one was diagnosed as squamous carcinoma metastasizing to the lung, and the other, as adenoma arising in the wall of a bronchus. Three examples of myeloid leukemia are included with the tumors. There were two tumors, namely, a lymphoid tumor and a fibroma, in each of 3

10. Bullock, F. D., and Curtis, M. R.: J. Cancer Research **14**:1, 1930.

11. Nelson, A. A., and Morris, H. J.: Arch. Path. **31**:578, 1941.

TABLE 7.—*Frequency of Chronic Nephrosis with Respect to Age*

Age in Days	Rats Examined	Rats with Chronic Nephrosis	Frequency of Chronic Nephrosis
Rats killed			
200 to 299	16	0	0
300 to 399	32	3	9.4%
500 to 620	16	6	37.5%
Rats that died			
Up to 599	25	8	32.0%
600 to 699	35	11	31.4%
700 to 799	50	30	60.0%
Over 800	23	10	43.5%

TABLE 8.—*Frequency of Chronic Nephrosis with Respect to the Experimental Groups Among Rats Killed*

Experimental Group	Rats Examined	Rats with Chronic Nephrosis	Frequency of Chronic Nephrosis
High protein	32	7	21.9%
Low protein	32	2	6.2%
Casein	32	7	21.9%
Liver	32	2	6.2%
Exercise	32	4	12.5%
No exercise	32	5	15.6%
Unrestricted diet	32	8	25.0%
Restricted diet	32	1	3.1%

TABLE 9.—*Frequency of Chronic Nephrosis with Respect to the Experimental Groups Among Rats That Died*

Experimental Group	Rats Examined	Rats with Chronic Nephrosis	Frequency of Chronic Nephrosis
High protein	66	36	54.5%
Low protein	67	23	34.5%
Casein	61	32	52.5%
Liver	72	27	37.5%
Exercise	74	31	41.9%
No exercise	59	28	47.5%
Unrestricted diet	63	33	52.4%
Restricted diet	70	26	37.1%

TABLE 10.—*Frequency of Chronic Nephrosis with Respect to Age and the Experimental Groups Among Rats Killed*

Age in Days	Rats Examined	Rats with Chronic Nephrosis	Frequency of Chronic Nephrosis	Rats Examined	Rats with Chronic Nephrosis	Frequency of Chronic Nephrosis
	High Protein Group			Low Protein Group		
200 to 399	24	3	12.5%	24	0	0
500 to 620	8	4	50.0%	8	2	25.0%
	Casein Group			Liver Group		
200 to 399	24	2	8.3%	24	1	4.2%
500 to 620	8	5	62.5%	8	1	12.5%
	Exercise Group			No Exercise Group		
200 to 399	24	1	4.2%	24	2	8.3%
500 to 620	8	3	37.5%	8	3	37.5%
	Unrestricted Diet Group			Restricted Diet Group		
200 to 399	24	3	12.5%	24	0	0
500 to 620	8	5	62.5%	8	1	12.5%

animals. Of the rats killed for examination, lymphoid tumors had developed in the lungs of 3 in the oldest age group. Table 13 shows the frequency of the different types of tumors and also the average age

TABLE 11.—*Frequency of Chronic Nephrosis in Relation to Protein Level, Type of Protein and Restriction of Diet Among Rats Killed*

Experimental Group	Rats Examined	Rats with Chronic Nephrosis	Frequency of Chronic Nephrosis
High casein unrestricted diet	8	4	50.0%
High casein restricted diet	8	1	12.5%
Low casein unrestricted diet	8	2	25.0%
Low casein restricted diet	8	0	0
High liver unrestricted diet	8	2	25.0%
High liver restricted diet	8	0	0
Low liver unrestricted diet	8	0	0
Low liver restricted diet	8	0	0

TABLE 12.—*Frequency of Chronic Nephrosis in Relation to Protein Level, Type of Protein and Restriction of Diet Among Rats That Died*

Experimental Group	Rats Examined	Rats with Chronic Nephrosis	Frequency of Chronic Nephrosis
High casein unrestricted diet	13	13	100.0%
High casein restricted diet	17	7	41.1%
Low casein unrestricted diet	16	7	43.7%
Low casein restricted diet	15	5	33.3%
High liver unrestricted diet	17	7	41.1%
High liver restricted diet	19	9	47.3%
Low liver unrestricted diet	17	6	35.3%
Low liver restricted diet	19	5	26.3%

TABLE 13.—*Frequency of Different Types of Tumor Among Rats That Died and the Average Age at Death of Tumor-Bearing Rats*

Type of Tumor	Tumors	Frequency of Tumors of Given Type in 151 Rats Examined	Average Age of Tumor-Bearing Rats	
			Days	Range, Days
Lymphoid tumors arising in thoracic organs	22	14.5%	704	553-875
Lymphoid tumors arising elsewhere	10	6.6%	676	512-822
Leukemic tissue (myeloid leukemia)	3	2.0%	742	622-814
Connective tissue tumors (fibroma, fibrosarcoma)	11	7.3%	718	476-832
Epithelial tumors (squamous cell carcinoma, adenoma)	2	1.3%	689	640-738

at death of rats with tumors. The average age at death bore no relation to the type of tumor.

Table 14 shows that there is an increase in frequency of tumors with advance in age. In table 15 it is seen that tumors were slightly more frequent in animals receiving a diet low in protein (liver) and exercise than in those receiving a diet high in protein (casein) and no exercise.

An analysis of the small groups in which these variables were combined showed that 11 of 22 rats fed the low liver diet and forced to exercise (groups 13 and 14 in table 1) bore tumors, a frequency of 50 per cent. In contrast, 3 of 17 rats fed the high casein diet and given no exercise (groups 3 and 4 in table 1) acquired tumors, a frequency of only 18 per cent. However, the average ages at death of the 22 rats on the low liver–exercise regimen and of the 17 rats on the high casein–no exercise regimen were 761 and 639 days, respectively. This difference in age

TABLE 14.—*Frequency of Tumor with Respect to Age*

Age in Days	Rats Examined	Rats Bearing Tumors	Frequency of Tumor
Rats killed			
200 to 299	16	0	0
300 to 399	32	0	0
500 to 620	16	3	18.7%
Rats that died			
Up to 599	32	6*	18.7%
600 to 699	45	14	31.1%
700 to 799	51	18*	35.3%
Over 800	23	7*	30.4%

* This includes 1 rat that had two separate tumors.

TABLE 15.—*Frequency of Tumors with Respect to the Experimental Groups Among Rats That Died*

Experimental Group	Rats Examined	Rats Bearing Tumors	Frequency of Tumor
High protein	75	18*	24.0%
Low protein	76	27†	35.5%
Casein	68	15*	22.1%
Liver	83	30†	36.0%
Exercise	78	27†	34.6%
No exercise	73	18*	24.6%
Unrestricted diet	75	21†	28.0%
Restricted diet	76	24*	31.6%

* This includes 1 rat that had two separate tumors.
† This includes 2 rats that had two separate tumors each.

at death probably accounts for the apparent influence of regimen on the development of tumors.

COMMENT

The observed frequency of chronic pneumonia suggests that this disease is an important cause of death in old rats. Its relation to the average life span has not been studied satisfactorily because no strain of rats examined thus far has been found to be free from the disease. A difference in frequency dependent on strain probably exists, but statistics for various strains are not available. Drummond and co-workers [12]

12. Drummond, J. C.; Baker, A. Z.; Wright, M. D.; Marrian, P. M., and Singer, E. M.: J. Hyg. **38**:356, 1938.

have found a difference in frequency within a single strain dependent on environment and bearing a relation to the average life span. Thus chronic pneumonia developed in 69 per cent of rats kept in one laboratory, and the average span of life was 84.6 weeks. In a different laboratory disease developed in 42 per cent of the rats of the same strain, and the average span of life was 112 weeks. It is uncertain if chronic disease of the lung modifies the length of life or if it occurs as the result of senescent changes. According to Klieneberger and Steabben,[7] the condition is never fatal within the ordinary life span of the rat. The disease is not seen in young rats, and these authors [7] failed to reproduce it in young animals. It seems probable that aging of the lung is one of the factors essential to its development.

In our experiment dietary factors which increased or diminished the average span of life did not alter the frequency of chronic pneumonia. Drummond and associates [12] found no change in the frequency of the disease in rats given a diet deficient in "vitamin B complex," although this diet shortened the average life span by about eight weeks. On the other hand, when the average life span of rats has been extended by giving a diet low enough in calories to retard growth, McCay and others have obtained both indirect [13] and direct [14] evidence that the frequency and severity of the disease are decreased.

The frequency of chronic nephrosis increased with advance in age. Our observations suggest that this lesion is primarily a destruction of the renal units through occlusion of the tubules by albuminous casts. Fibrosis may subsequently take place. It is possible that long-continued excretion of albumin would produce such a lesion. McCay and Nelson,[15] Jackson and Riggs [16] and Bell [17] have noted albumin in the urine of seemingly normal rats, and McCay and co-workers [1] have shown that the amount excreted may be proportional to the level of protein in the diet. In our supplementary experiments albumin was found in the urine of mature rats with histologically normal kidneys. In the urine of rats subsequently found to have chronic nephrosis the amount of albumin was increased and was roughly correlated with the extent of renal damage. Albuminuria may thus not only precede the development of the lesions but may increase as a consequence of this type of renal damage. These observations may explain in part the greater frequency of chronic nephrosis in rats on high protein diets as con-

13. McCay, C. M.; Ellis, G. H.; Barnes, L. L.; Smith, C. A. H., and Sperling, G.: J. Nutrition **18**:15, 1939.

14. Saxton, J. A., Jr.: New York State J. Med. **41**:1095, 1941.

15. McCay, C. M., and Nelson, V. E.: J. Metab. Research **7-8**:199, 1925-1926.

16. Jackson, H., Jr., and Riggs, M. D.: J. Biol. Chem. **67**:101, 1926.

17. Bell, M. E.: J. Physiol. **79**:191, 1933.

trasted with those on low protein diets. However, not only a high level of protein but also the use of casein as the source of protein and an unrestricted diet each independently favored development of the disease. If the disease results solely from the excretion of albumin, then other dietary conditions besides a high level of protein in some way influence the amount excreted. Further study is necessary to find whether excretion of albumin is a normal response of the rat to certain conditions of diet, and to clarify the relation of the excretion of albumin to the development of chronic nephrosis.

McCay and associates [1] have found that the average life span of rats fed the liver diets of this experiment was significantly greater than that of rats fed the casein diets and that on the average the animals moderately restricted in body weight outlived those allowed all the food they would eat. It is noteworthy that chronic nephrosis was less frequent in the groups with the longer life spans. Certain combinations of experimental factors were shown by McCay and associates to produce a significant increase in the average life span and chronic nephrosis was less common when the life span was greater. For example, with a high protein diet rats whose source of protein was liver outlived those whose source was casein. Table 12 shows that chronic nephrosis developed in 16 (44 per cent) of the 36 examined rats which had been fed a diet with a high liver content whereas this disease developed in 20 (66 per cent) of 30 rats on a diet with a high casein content. The group which McCay and associates found to have the longest average life span was fed a restricted diet low in liver and forced to exercise (group 13 in table 1). Of this group, 11 animals were examined, and only 3 (27 per cent) had chronic nephrosis. In contrast, this disease was present in all of 7 examined rats which had been fed an unrestricted diet high in casein and given no exercise (group 4 in table 1).

In view of these relations of diet to the average length of life and to the frequency of the renal lesions it is probable that the diets produced their effects on the life span through their effects on the kidneys. However, although tables 8 and 9 show that chronic nephrosis was more common in rats on high protein diets than in those on low protein diets, the average life span was not significantly altered by the protein level. The suggestion is offered that the high protein diets may exert on the animals some other influence which compensates for their effects on the kidneys.

With regard to the role of casein and liver in the production of dietary nephritis, Blatherwick and Medlar,[18] Medlar and Blatherwick,[19] Newburgh and Curtis [20] and others have found that casein is less inju-

18. Blatherwick, N. R., and Medlar, E. M.: Arch. Int. Med. **59**:572, 1937.
19. Medlar, E. M., and Blatherwick, N. R.: Am. J. Path. **13**:881, 1937.
20. Newburgh, L. H., and Curtis, A. C.: Arch. Int. Med. **42**:801, 1928.

rious to the rat kidney than some other forms of animal protein, such as beef muscle and liver. The renal lesions described by these authors appear to be different from the nephrosis described here. Medlar and Blatherwick after unilateral nephrectomy found lesions in the remaining kidney consisting of: sclerosis of glomeruli following initial injuries to the filter beds with or without obliteration of the capsular spaces; interstitial fibrosis; chronic inflammation; a variable but occasionally extensive cystic dilatation of proximal convoluted tubules. The lesions described by Newburgh and Curtis also appear to be characterized by primary glomerular injury and subsequent fibrosis. The protein levels in the experiments cited were generally higher than those of our experiment, and, when stated, the ages of the rats at the start were lower. These differences in procedure and type of renal damage appear to preclude an exact comparison of this experiment with the work cited.

The various tumors encountered showed a definite increase in frequency with advance in age. Of particular interest in this series was the preponderance of lymphoid tumors arising in the lungs. Our observations agree with those of Nelson and Morris [11] as to the frequency of tumors of this type in rats of the Osborne-Mendel strain. Ratcliffe [21] recorded 1 mediastinal lymphoblastoma and 3 neoplasms arising from thymus glands in 273 rats of the Wistar Institute strains showing external evidence of tumors. In the large series of tumors in rats reported by Bullock and Curtis [10] many of the lymphoid tumors described arose from intrathoracic sites, but the majority had their origin in the mesentery. Strain characteristics of the rats may be responsible for this difference.

It seems possible that the development of intrathoracic lymphoid tumors may be related to the lymphoid hyperplasia commonly found associated with chronic pneumonia of rats. Chronic pneumonia was seen in association with intrathoracic lymphoid tumors in 20 of the 22 cases cited in table 13. In the other 2 cases there was not sufficient pulmonary tissue examined to rule out chronic infection.

SUMMARY

A study has been made of the most common spontaneous diseases in 215 albino rats of the Yale (Osborne-Mendel) strain used in an experiment undertaken to determine the effect during the latter half of life of high (33-41 per cent) or of low (7-10 per cent) levels of casein or of liver, of moderate restriction of body weight by limiting the diet and of exercise. The frequency of these diseases has been tabulated with respect both to age and to modification of diet.

21. Ratcliffe, H. L.: Am. J. Path. **16**:237, 1940.

The most common diseases encountered were in order of frequency: chronic pneumonia with bronchiectasis; chronic nephrosis characterized by parenchymatous degeneration following obstruction of renal units by albuminous casts; various types of tumors, a large part of them diagnosed as lymphosarcoma, arising within the lungs. Each of these diseases occurred with sufficient frequency as age advanced to exert an unfavorable influence on the average span of life.

The frequency of chronic pneumonia and of tumors bore no direct relation to modifications of diet during the latter half of life, although some of these modifications altered significantly the average life span.

The frequency of chronic nephrosis was greater in animals on diets in which protein was supplied by casein than in animals on diets in which liver was the chief source of protein. Its frequency was greater in rats that received diets high in these proteins than in those on diets low in protein. The disease was more common in animals allowed to reach a normal weight as contrasted with those kept moderately underweight. As the frequency of chronic nephrosis was greater and the average life span shorter in animals that received casein as the protein of the diet and in animals allowed to reach a normal weight, the experiments indicate that injury to the kidney was increased by these diets in the latter half of life and that this shortened the span of life.

UNILATERAL RENAL ATROPHY ASSOCIATED WITH HYPERTENSION

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In recent years, numerous cases of unilateral renal disease associated with hypertension have been reported in which relief of hypertension has been obtained for varying intervals by nephrectomy or other surgical procedures on the kidney.[1] The renal lesions in the reported cases included pyelonephritis, hydronephrosis, congenital anomalies, infarcts and aneurysm of the renal artery. These cases are particularly interesting since in the dog unilateral renal ischemia in the presence of an intact opposite kidney generally produces only a transient elevation in blood pressure.[2] Wilson and Byrom[3] recently found, however, that unilateral renal ischemia produced permanent hypertension among rats.

Although it has been demonstrated both clinically and experimentally that hypertension may occur as a result of unilateral renal disease, few studies have been made in an attempt to determine how often the two conditions are associated.

From the Section on Pathologic Anatomy (Dr. Baggenstoss) and the Division of Medicine (Dr. Barker), Mayo Clinic.

1. (*a*) Butler, A. M.: J. Clin. Investigation **16**:889, 1937. (*b*) Barker, N. W., and Walters, W.: Proc. Staff Meet., Mayo Clin. **13**:118, 1938. (*c*) Leadbetter, W. F., and Burkland, C. E.: J. Urol. **39**:611, 1938. (*d*) Boyd, C. H., and Lewis, L. G.: ibid. **39**:627, 1938. (*e*) Crabtree, E. G.: Tr. Am. A. Genito-Urin. Surgeons **31**:299, 1938. (*f*) Barney, J. D., and Suby, H. I.: New England J. Med. **220**:744, 1939. (*g*) McIntyre, D. W.: J. Urol. **41**:900, 1939. (*h*) Nesbitt, R. M., and Ratliff, R. K.: ibid. **43**:427, 1940. (*i*) Schroeder, H. A., and Fish, G. W.; Am. J. M. Sc. **199**:601, 1940. (*j*) Oppenheimer, B. S.; Klemperer, P., and Moschkowitz, M. D.: Tr. A. Am. Physicians **54**:69, 1939. (*k*) Kerr, W. J., in discussion on Oppenheimer and others.[1j] (*l*) Hyman, A., in discussion on Crabtree, E. G., and Prien, E. L.: J. Urol. **42**:982, 1939. (*m*) Morton, W. P., in discussion on Crabtree, E. G., and Prien, E. L.: ibid. **42**:982, 1939. (*n*) Bartels, E. C., and Leadbetter, W. F.: Bull. Lahey Clin. **1**:17, 1940. (*o*) Patch, F. S.; Rhea, L. J., and Codnere, J. T.: Canad. M. A. J. **43**:419, 1940. (*p*) Howard, T. L.; Forbes, R. P., and Lipscomb, W. R.: J. Urol. **44**:808, 1940. (*q*) Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Am. J. Dis. Child. **61**:128, 1941.

2. Goldblatt, H.: Am. J. Clin. Path. **10**:40, 1940.

3. Wilson, C., and Byrom, F. B.: Lancet **1**:136, 1939.

In a study of a series of 57 consecutive cases in which a diagnosis of chronic atrophic pyelonephritis was made by urographic examination, Walters and one of us (Barker [4]) found that in 26 (45.6 per cent) the blood pressure was more than 145 systolic and 90 diastolic as measured in millimeters of mercury. Braasch, Walters and Hammer [5] found that of 43 patients operated on for atrophic pyelonephritis, hypertension (i. e., a blood pressure of 145 systolic and 90 diastolic or more) affected 20 (46.5 per cent). They also found that hypertension was present in 161 (20.3 per cent) of 793 cases of renal stone, in 51 (14 per cent) of 372 cases of hydronephrosis without stone, in 12 (7.6 per cent) of 158 cases of renal tuberculosis and in 38 (27.7 per cent) of 137 cases of renal adenocarcinoma. In 975 consecutive cases in which the records were taken at random from the files of the Mayo Clinic, the incidence of hypertension was 20 per cent. Of the patients who were less than 50 years of age, 9.1 per cent had hypertension, while of those who were 50 years of age or more, 37.9 per cent had this complication.

Crabtree and Chaset [6] found blood pressure readings of more than 150 mm. systolic and 100 mm. diastolic in only 14 (9.3 per cent) of 150 cases of unilateral renal disease. In the hypertensive group there were 6 instances of hypernephroma, 7 of chronic pyelonephritis and 1 of tuberculous pyelonephritis.

So far as we are aware, there have been no comparable studies of cases encountered at necropsy. We thought that such a study would be worth while as a check on the results obtained by clinical and surgical surveys. Furthermore, there are certain advantages in studying a series of cases at necropsy, as it is possible to check the diagnosis of hypertension arrived at by evaluations of the blood pressure with the actual weight of the heart. Another advantage is that the condition of the opposite kidney, especially in regard to the presence of inflammation and arteriosclerosis, can be determined accurately.

DIAGNOSIS OF HYPERTENSION

In this study hypertension was considered present when the blood pressure in millimeters of mercury was 150 systolic and 90 diastolic or more and the heart hypertrophied. A diagnosis of cardiac hypertrophy was made when the weight of the heart was greater than the theoretic mean normal weight for the weight of the body and the sex as determined in the tables of H. L. Smith.[7] The diagnosis of hypertension was not

4. Barker, N. W., and Walters, W.: J. A. M. A. **115**:912, 1940.

5. Braasch, W. F.; Walters, W., and Hammer, H. J.: J. A. M. A. **115**: 1837, 1940.

6. Crabtree, E. G., and Chaset, N.: J. A. M. A. **115**:1842, 1940.

7. Smith, H. L.: Am. Heart J. **4**:79, 1928.

made on the basis of determinations of blood pressure of 150 mm. systolic and 90 mm. diastolic or more alone. Some degree of cardiac hypertrophy was present in each instance. In some cases, however, hypertension was considered present even though normal or subnormal blood pressure determinations were obtained before death, for example, in instances of coronary occlusion, cardiac decompensation and shock. In such cases a diagnosis of hypertension was made only if the weight of the heart was 50 Gm. or more than the maximal theoretic normal weight as determined for the weight of the body and the sex in the tables of H. L. Smith. In this group cardiac hypertrophy was considered a result of hypertension only after all other known causes of cardiac enlargement, such as valvular or pericardial disease, hyperthyroidism, glomerulonephritis and so forth, were ruled out.

The diagnosis of hypertension was made or excluded on the basis of the weight of the heart alone in 29 cases. In the remaining 68 cases

TABLE 1.—*Causes of Death in Cases of Unilateral Renal Atrophy*

	Pyelonephritic Atrophy	Hydronephrotic Atrophy	Pyonephrotic Atrophy	Hypoplasia
Neoplasm	12	16	2	4
Infection	17	5	2	3
Arteriosclerosis	3	3	1	1
Hypertension	4	1	..	..
Hypertrophy of prostate	5	2	..	..
Miscellaneous	7	1	3	5
Uremia present	7	0	1	0

blood pressure of 150 mm. or more systolic or 90 or more diastolic was present in addition to cardiac hypertrophy.

MATERIAL

This study was made of 84 cases of unilateral renal atrophy and 13 of unilateral hypoplasia, a total of 97 cases in which necropsy was performed. There were 48 cases of pyelonephritic atrophy, 28 cases of hydronephrotic atrophy and 8 cases of pyonephrotic atrophy. The causes of death in this group are summarized in table 1. In the overwhelming majority of these cases the presence of unilateral renal atrophy was an incidental finding at necropsy and was not recognized before death. As can be seen in table 1, neoplastic disease and various types of infection were the commonest causes of death. The infections included pneumonia, meningitis, pelvic inflammatory disease, appendicitis and renal infections. Inflammation of the opposite kidney was a cause of death in 5 of the cases in which pyelonephritic atrophy was present and in 2 cases each of hydronephrotic atrophy and pyonephrotic atrophy.

Hypertension was considered a cause of death in 5 cases, and uremia was present in 8 cases only.

CONTROL SERIES

In the group with unilateral renal atrophy the percentage of patients in each decade of life at the time of death was determined. For the control group 100 cases encountered at necropsy were taken at random except that the percentage of patients in each decade was the same as in the group studied. The diagnosis of hypertension was made or excluded in these cases by the same criteria used in the cases of unilateral renal atrophy. The incidence of hypertension in this series of control cases was 29 per cent.

RESULTS

The incidence of hypertension in the cases of each type of unilateral renal atrophy and in the cases of unilateral hypoplasia is recorded in table 2. Only in the cases of pyelonephritic atrophy and those of pyonephrotic atrophy was the incidence of hypertension greater than in the control group.

In order to determine whether the degree of atrophy influenced the incidence of hypertension, the cases of pyelonephritic and those of hydronephrotic atrophy were divided into two groups on the basis of the weight of the atrophied kidney. One group consisted of all cases in which the atrophied kidney weighed 75 Gm. or less and the other group consisted of all cases in which the kidney weighed more than 75 Gm. In table 3 the cases of pyelonephritic atrophy are classified in this way together with data relative to sex and age. Although the figures are of questionable statistical significance because of the small numbers of cases, they suggest that hypertension is more likely to be present in those cases in which unilateral pyelonephritic atrophy is of severe degree. There were more women who had unilateral pyelonephritic atrophy than men, although in routine necropsies at the Mayo Clinic males predominate 2 to 1. In the group in which the atrophied kidneys weighed more than 75 Gm., the mean age of the patients who had hypertension was almost nineteen years more than that of the patients who did not have hypertension. All patients who had hypertension were more than 50 years of age. Consequently, the incidence of hypertension (35.4 per cent) in this group is probably accounted for by the increased age of the

TABLE 2.—*Incidence of Hypertension*

	Cases	Hypertension, per Cent
Control group	100	29.0
Pyelonephritic atrophy	48	39.6
Hydronephrotic atrophy	28	25.0
Pyonephrotic atrophy	8	37.5
Hypoplasia	13	15.3

patients. Braasch and co-workers,[5] for instance, found that 37.9 per cent of an unselected group of patients more than 50 years of age had hypertension, i. e., blood pressure of 145 mm. systolic and 90 mm. diastolic or more.

The hearts of the patients who had hypertension were hypertrophied (table 3). The mean weight of the atrophied and that of the opposite

TABLE 3.—*Unilateral Pyelonephritic Atrophy (Forty-Eight Cases)*

	Kidney: 75 Gm. or Less (31 Cases)		Kidney: More Than 75 Gm. (17 Cases)	
	Hypertension	No Hypertension	Hypertension	No Hypertension
Cases	13 (41.9%)	18 (58.1%)	6 (35.4%)	11 (64.6%)
Men	6	6	4	6
Women	7	12	2	5
Mean age, years	51.9	53.8	66.3	47.7
Patients more than 50 years	7	9	6	4
Mean weight, Gm.				
Heart	441.3	322.8	506.3	325.8
Atrophic kidney	46.8	50.4	88.3	99
Opposite kidney	277.3	224.4	210.3	222.6

TABLE 4.—*Unilateral Hydronephrotic Atrophy (Twenty-Eight Cases)*

	Kidney: 75 Gm. or Less		Kidney: More Than 75 Gm.	
	Hypertension	No Hypertension	Hypertension	No Hypertension
Cases	3 (21.4%)	11 (78%)	4 (28.5%)	10 (71.5%)
Men	2	8	1	6
Women	1	3	3	4
Mean age, years	56.6	53	64.5	53.7
Patients more than 50 years	2	7	4	6
Mean weight, Gm.				
Heart	539	297.1	385.5	311.8
Atrophic kidney	61.3	57.4	101.5	107.8
Opposite kidney	184	230.3	210	212.8

kidneys also are recorded in this table. The fact that the opposite kidney was hypertrophied in practically every case indicates that the degree of renal atrophy was great enough and of sufficient duration to bring about compensatory hypertrophy of the opposite kidney.

In table 4 the cases of unilateral hydronephrotic atrophy are analyzed similarly. In this group of cases the incidence of hypertension was lower in the cases of severe atrophy. The cases are, however, too few and the differences too small to be significant.

In table 5 the cases of unilateral pyonephrotic atrophy are analyzed. The incidence of hypertension (37.5 per cent) approaches that in the cases of pyelonephritic atrophy. In this group, however, the mean age of the patients who had hypertension was seventeen years more than that of the patients who did not have hypertension. All patients who had hypertension were more than 50 years of age. The causes of hydronephrosis in the cases of hydronephrotic and pyonephrotic atrophy are listed in table 6.

TABLE 5.—*Unilateral Pyonephrotic Atrophy (Eight Cases)*

	Hypertension	No Hypertension
Cases	3 (37.5%)	5 (62.5%)
Men	2	4
Women	1	1
Mean age, years	69.6	52.4
Patients more than 50 years	3	4
Mean weight, Gm.		
Heart	430	259.2
Atrophic kidney	197	82.2
Opposite kidney	241.2	210.2

TABLE 6.—*Cause of Hydronephrosis*

	Unilateral Hydronephrotic Atrophy (28 Cases)		Unilateral Pyonephrotic Atrophy (8 Cases)	
	Hypertension	No Hypertension	Hypertension	No Hypertension
Neoplasm	3	11	0	0
Stones	1	2	3	2
Stenosis	1	4	0	1
Kink	1	1	0	0
Idiopathic type	1	3	..	2
Total	7	21	3	5

There were 13 cases of unilateral renal hypoplasia; hypertension was present in only 2 instances (15.3 per cent). All the patients were men; the mean age of the patients who had hypertension was 52.5 years. The mean age of those who did not have hypertension was 43.8 years. The mean weight of the hypoplastic kidneys in the cases of hypertension was 77.5 Gm.; in the nonhypertensive group the mean weight was 44.4 Gm. The mean weights of the opposite kidneys for each group were 219 Gm. and 211.4 Gm., respectively.

PATHOLOGIC ANATOMY

Pyelonephritic Atrophy.—The gross appearance of the kidneys in the cases of pyelonephritic atrophy varied. The majority were badly

scarred and deformed; others had fewer and smaller scars. Several were finely nodular, and a few had smooth surfaces. In general, the scars were depressed, flattened regions, but occasionally they were V shaped and identical with those produced by infarcts. Dilatation of the pelvis was not a prominent feature of these kidneys, although slight degrees of dilatation were common. This finding was expected since obstruction of the urinary passages was not often present in these cases. Stones, either in the kidneys or the ureters, were present in only 5 cases and had caused obstruction and dilatation of the pelvis in only 3. Hypertrophy of the prostate gland sufficient to cause obstruction was present in 5 cases.

The histologic appearance of the kidneys in cases of pyelonephritic atrophy also was variable. No attempt will be made to give a complete description of the histologic characteristics of the kidneys in these cases. Excellent descriptions of pyelonephritic atrophy have been given by Staemmler and Dopheide,[8] Putschar,[9] Fahr,[10] Weiss and Parker[11] and Mallory, Crane and Edwards.[12] The histologic diagnostic criteria outlined by these workers were used in confirming the diagnosis made from the gross appearance in these cases. In general, the cases could be placed in one of two groups. In one group the histologic appearance was dominated by the presence of dilated tubules and cystlike spaces which contained a homogeneous eosinophilic substance, the so-called colloid casts. Associated with this "thyroid-like" appearance, there were fibrosis of the pyramids and hyalinization or complete disappearance of the glomeruli. In some kidneys of this group this appearance was present only in focal scarred regions, while in other kidneys of the group practically the entire parenchyma was replaced by nonfunctioning tissue with this appearance (fig. 1 *a* and *b*). In the other group the histologic appearance was dominated by severe atrophy of the tubules, many of which appeared to be collapsed and nonfunctioning (fig. 2 *a* and *b*). There was a diffuse increase in lymphocytes and generally periglomerular

8. Staemmler, M., and Dopheide, W.: Virchows Arch. f. path. Anat. **277**: 713, 1930.

9. Putschar, W.: Die entzündliche Erkrankungen der ableitenden Harnwege und der Nierenhüllen einschliesslich der Pyelonephritis und der Pyonephrose. Pathogenese der Pyelitis und Pyelonephritis, in Lubarsch, O., and Henke, F.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1934, vol. 6, pt. 2, p. 401.

10. Fahr, T.: Virchows Arch. f. path. Anat. **301**:140, 1938.

11. Weiss, S., and Parker, F., Jr.: Medicine **18**:221, 1939.

12. Mallory, G. K.; Crane, A. R., and Edwards, J. E.: Arch. Path. **30**: 330, 1940.

fibrosis and hyalinization of the glomeruli were present. In some instances the glomeruli appeared fairly normal. In some kidneys both types of histologic change were present. No correlation was found between any histologic pattern and the incidence of hypertension.

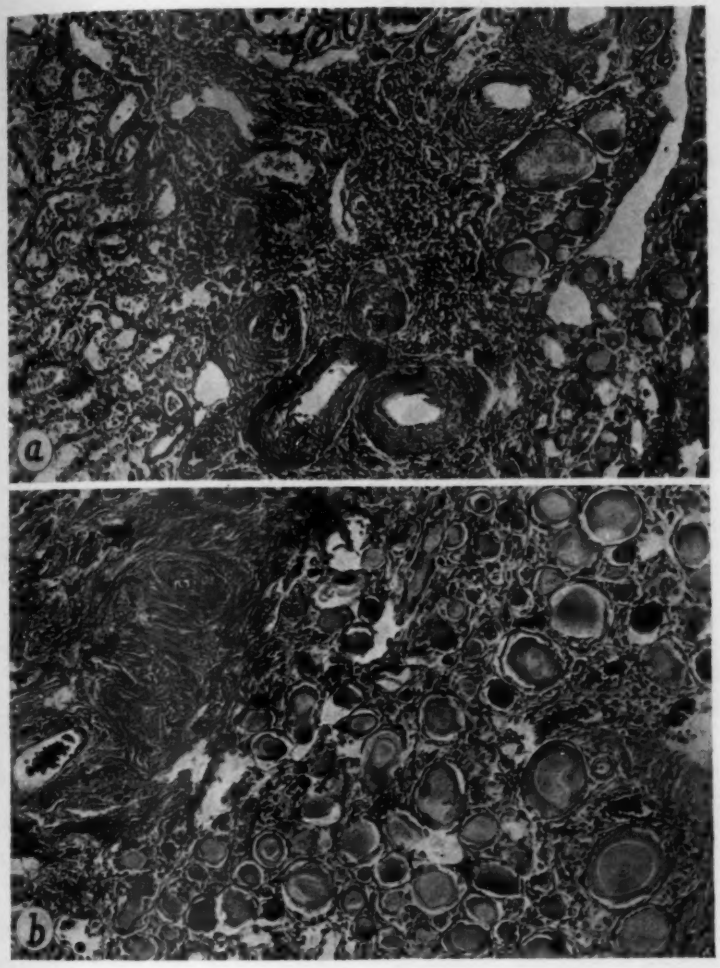

Fig. 1.—Pyelonephritic atrophy with arteriosclerosis, parenchymal atrophy, fibrosis and colloid casts. (*a*) The patient had hypertension (hematoxylin and eosin; × 100). (*b*) The patient did not have hypertension (hematoxylin and eosin; × 100).

In most of the cases of pyelonephritic atrophy, some portion of the atrophied kidney showed collections of lymphocytes and occasionally plasma cells, and the kidney was considered to be the seat of chronic active inflammation, although in most of these instances the lesions were

retrogressive rather than progressive and in some instances, perhaps, the presence of lymphocytes did not indicate inflammation. The presence or absence of inflammatory processes and the type present are indicated in table 7. The character of the inflammatory process did not appear to influence the incidence of hypertension.

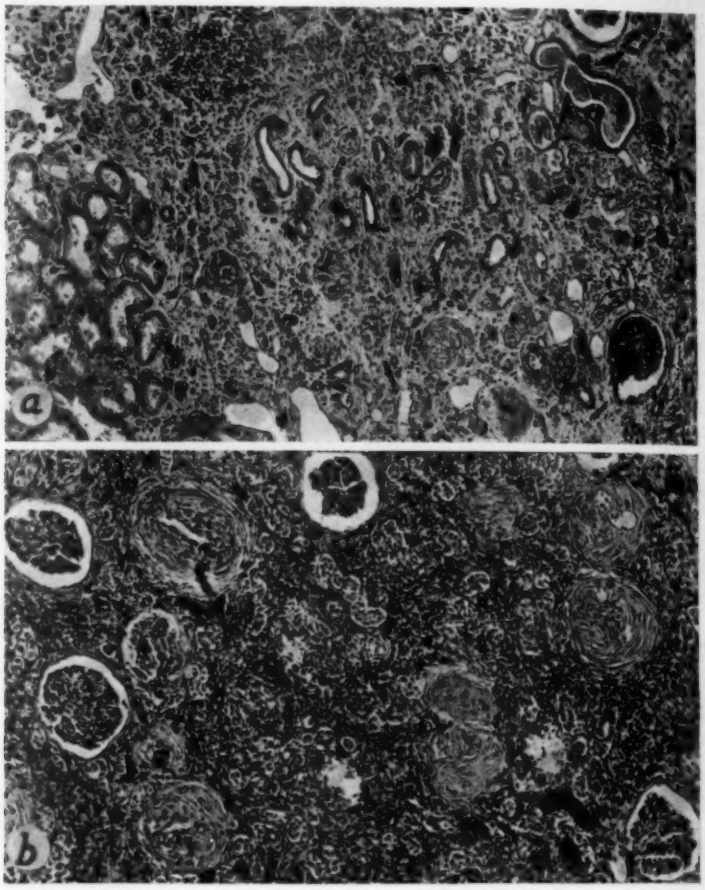

Fig. 2.—Pyelonephritic atrophy with arteriosclerosis, interstitial lymphocytes and atrophy of tubules. (*a*) The patient had hypertension (hematoxylin and eosin; × 75). (*b*) The patient did not have hypertension (hematoxylin and eosin; × 75).

Table 7 presents data concerning inflammation in the opposite kidney in the cases of pyelonephritic atrophy and the cases of hydronephrotic atrophy. Although the opposite kidney often was the seat of an inflammatory process, it was never atrophied; as a rule it was markedly hyper-

trophied. In the cases with hypertension the opposite kidney was more often the seat of an inflammatory process than in the cases in which hypertension was absent.

Thickening of the arterial walls in the scarred portions of the kidneys in the cases of pyelonephritic atrophy was generally graded 1 to 3 (grading was on the basis of 1 to 4, in which 4 was the most extensive); the arteries in the portions that were not scarred were either normal or revealed less sclerosis than those in the scars. This was true of the cases in which hypertension was an associated feature as well as in those in which it was not. In the larger arteries the most prominent change

TABLE 7.—*Inflammation in Atrophic Kidney and Opposite Kidney*

Inflammation	Pyelonephritic Atrophy		Hydronephrotic Atrophy	
	Hypertension	No Hypertension	Hypertension*	No Hypertension
Inflammation in Atrophic Kidney				
None	0	0	0	4
Healed	4	5	0	2
Chronic	12	21	6	14
Acute	0	0	0	0
Recurrent	3	3	0	1
Total	19	29	6	21
Inflammation in Opposite Kidney				
None	9	19	1	12
Chronic	6	6	4	1
Acute	3	3	1	6
Recurrent	1	1	0	0
Total	19	29	6†	19†

* In 1 case the specimen was not saved.

† In 3 cases of hydronephrotic atrophy the specimen of the opposite kidney was not saved.

was elastic reduplication. Splitting and fraying of the elastic laminas and often an excessive amount of folding occurred (fig. 3). Concurrently, atrophy of the muscular elements of the media and proliferation of the intimal connective tissue often were found. Hyaline changes in the media were also a common finding. In the small arteries and arterioles, hypertrophy of the media was occasionally seen, and hyaline changes were common. The only change observed in the afferent glomerular arterioles was hyaline thickening, and this was not common in the atrophied kidneys in either group.

When the arterial changes in the atrophied kidneys in the cases of hypertension and pyelonephritic atrophy were compared with those in

the cases in which hypertension was absent, no significant differences could be detected, for in general the same changes occurred in both groups. After the changes in the arterial walls had been graded in each case, it was found that severe arteriosclerosis was present in a greater percentage of cases in the hypertensive group than in the nonhypertensive group. It was impossible, however, to determine whether or not hypertension was associated in any given case by an examination of the arteries of the atrophied kidney.

The arteries of the opposite kidneys also were studied carefully. In table 8 the degree of arteriosclerosis is compared with that of the atrophied kidneys. In 8 of 19 cases of pyelonephritic atrophy and hyper-

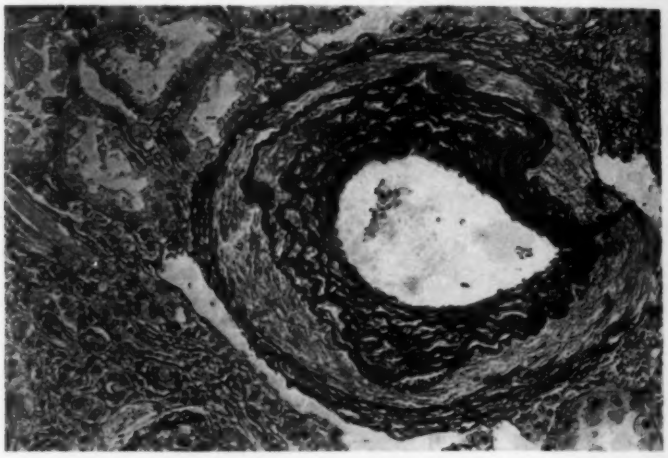

Fig. 3.—Arterial changes in pyelonephritic atrophy; elastic reduplication and atrophy of the muscular elements of the media (elastin H; × 150).

tension and in 2 of 7 cases of hydronephrotic atrophy and hypertension, the arteries in the nonatrophied kidney were considered normal.

Hydronephrotic Atrophy.—The common histologic finding in the hydronephrotic kidneys was diffuse atrophy of the tubules with varying amounts of fibrosis and collections of lymphocytes (fig. 4 *a* and *b*). In some instances, groups of dilated tubules were seen, and occasionally a "thyroid-like" transformation of the renal substance, which is common in pyelonephritic atrophy, was present. Some form of inflammation was present in all but 4 cases of hydronephrotic atrophy (table 7). In 1 case, however, the specimen was not available for study. In these cases, also, collections of lymphocytes often were the only criterion on which a diagnosis of chronic inflammation was based. Generally, some

degree of periglomerular fibrosis also was present, and varying numbers of glomeruli were hyalinized. In the intact glomeruli, the capillary tufts generally appeared compressed, and the capsular space often was dilated.

The arteries in the atrophied kidneys in the cases with hypertension were generally more sclerotic than those in the cases in which hypertension was not present. The vascular changes were practically of the same type as those described in the kidneys with pyelonephritic atrophy.

The incidence and the type of inflammation present in the opposite kidney are recorded in table 7. The cases with hypertension had a higher incidence of active inflammation in the opposite kidney. The significance of this fact is difficult to evaluate.

The condition of the arteries in the opposite, nonatrophic kidneys is compared with reference to the presence or absence of hypertension in the cases of hydronephrotic atrophy in table 8.

TABLE 8.—*Degree of Arteriosclerosis in Opposite Kidney*

Arteries	Unilateral Pyelonephritic Atrophy		Unilateral Hydronephrotic Atrophy *	
	Hypertension	No Hypertension	Hypertension	No Hypertension
Normal	8	20	2	12
Sclerotic				
Same degree of arteriosclerosis as in affected kidney	3	4	2	3
Less than in affected kidney	8	5	2	4
Total	19	29	6	19

* In 3 cases no specimens were saved.

Pyonephrotic Atrophy.—In the group of cases of unilateral pyonephrotic atrophy destruction of the renal parenchyma was more severe than in the group of cases of unilateral hydronephrotic atrophy. In general, the histologic appearance was similar to that seen in cases of severe pyelonephritic atrophy (fig. 5 *a* and *b*). Active chronic inflammation was present in all but 1 case. Arteriosclerosis, grade 2 or 3, was always present in the scarred regions of the atrophied kidneys. In the normal tissue, when any was present, either the arteries were normal or the degree of arteriosclerosis was less. The degree of arteriosclerosis was as severe in the cases in which hypertension was not present as in the cases with hypertension.

In 4 of the 8 cases of pyonephrotic atrophy there was no evidence of inflammation in the opposite kidney. In 3 cases acute inflammation was present, and in 1 case, chronic inflammation. In only 1 case was the degree of arteriosclerosis in the opposite kidney as severe as that

in the diseased kidney. In 5 cases the degree of arteriosclerosis was less, and in 2 cases the arteries were considered normal for the age of the patient. Hypertension was not present in either of the latter 2 cases.

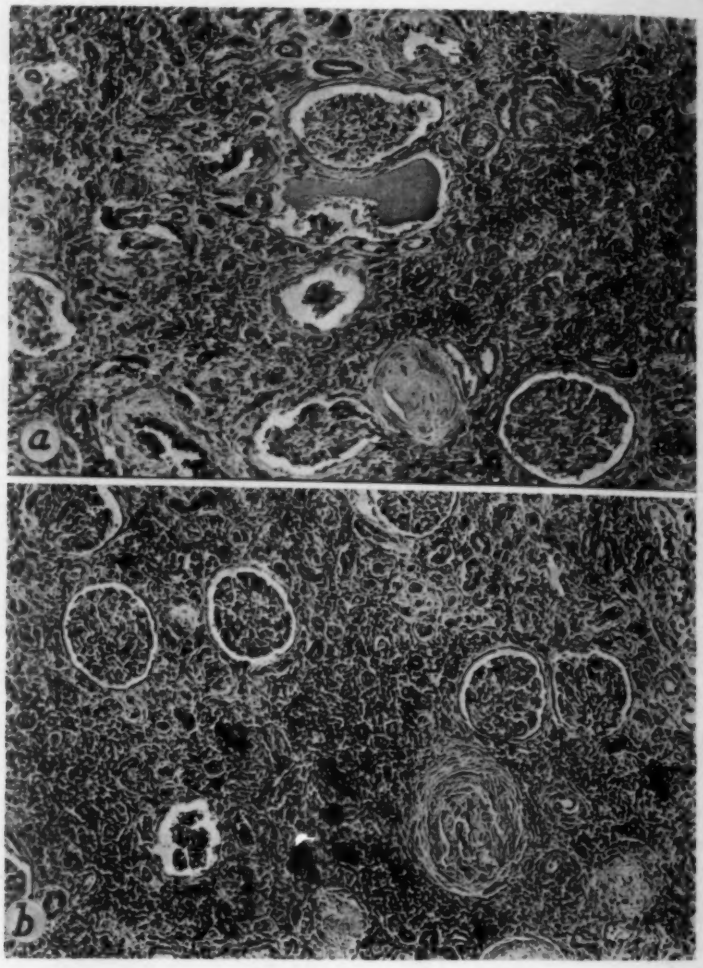

Fig. 4.—Hydronephrotic atrophy, atrophy of tubules and increased numbers of lymphocytes and hyalinized glomeruli. (*a*) The patient had hypertension (hematoxylin and eosin; × 100). (*b*) The patient did not have hypertension (hematoxylin and eosin; × 100).

Hypoplasia.—The hypoplastic kidneys were of two histologic types. There were 7 cases in which the histologic structure was normal and 6 cases in which there was evidence of maldevelopment and disorgani-

zation. In these cases, there was often an absence of glomeruli, and the tubules were widely dilated, abnormal structures surrounded by concentric rings of connective tissue and smooth muscle. In none of the cases of hypoplasia in which this histologic structure was present was hypertension associated.

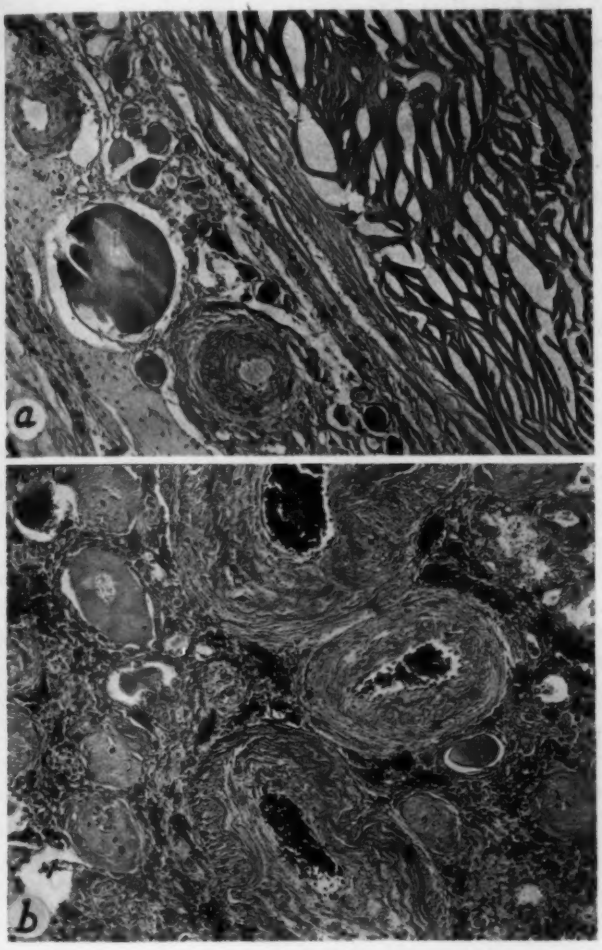

Fig. 5.—Pyonephrotic atrophy with arteriosclerotic destruction and hyalinization of glomeruli and dilated tubules. (*a*) The patient had hypertension (hematoxylin and eosin; × 80). (*b*) The patient did not have hypertension (hematoxylin and eosin; × 100).

There was evidence of chronic inflammation in the hypoplastic kidney in only 2 cases. The arteriosclerosis was graded 2 to 3 in the 2 cases with hypertension. Of the cases in which hypertension was not present,

the arteries were considered normal in 5. In the remaining 6 cases the arteriosclerosis and arteriolosclerosis ranged from grade 1 to grade 3.

There was no evidence of inflammation in the opposite kidney in any of the cases of unilateral hypoplasia. In the 2 cases with hypertension the arteries in the opposite kidney revealed the same degree of arteriosclerosis and arteriolosclerosis as those of the hypoplastic kidney. In 9 of the cases in which hypertension was not present, the arteries in the opposite kidney appeared normal; in 1 case the same degree of sclerosis was present, and in 1 case there was less sclerosis than in the hypoplastic kidney.

COMMENT

Although the figures are of questionable statistical significance because of the small numbers of cases, they at least suggest that unilateral pyelonephritic atrophy is more often associated with hypertension than would be expected on the basis of chance. In this regard the results are in agreement with similar studies by Walters and one of us (Barker) and by Braasch, Walters and Hammer, who studied clinical and surgical material. Only in the group of cases in which the pyelonephritic atrophy was severe and the kidney weighed 75 Gm. or less was the incidence of hypertension significantly more than might be expected. Hydronephrotic atrophy apparently did not influence the incidence of hypertension. The mean weight of the kidneys in cases of hydronephrotic atrophy was greater than the mean weight of the kidneys in the cases of pyelonephritic atrophy. The fact that the hydronephrotic kidneys were less atrophied may be responsible in part for the lower incidence of hypertension in these cases. Nevertheless, in the cases of hydronephrotic atrophy in which the atrophied kidney weighed more than 75 Gm. a higher incidence of hypertension was present than in those cases in which the kidney weighed 75 Gm. or less (table 4).

In about 53 per cent of the cases of pyelonephritic atrophy and 83.4 per cent of the cases of hydronephrotic atrophy and hypertension evidence of inflammation was present in the opposite kidney. In only about 34 per cent of the cases of pyelonephritic atrophy and 36.9 per cent of the cases of hydronephrotic atrophy in which hypertension was absent was inflammation present in the opposite kidney. It is difficult to evaluate the influence of inflammation of the opposite kidney on the incidence of hypertension. There was no evidence of glomerulonephritis in any case.

In 8 of the 19 cases (42 per cent) of pyelonephritic atrophy and hypertension the arteries and arterioles in the opposite kidney were considered normal for the age of the patient. At first sight this finding seems to be at variance with the studies of Fishberg,[13] Bell and Clawson[14] and

13. Fishberg, A. M.: Arch. Int. Med. **35**:650, 1925.
14. Bell, E. T., and Clawson, B. J.: Arch. Path. **5**:939, 1928.

Moritz and Oldt [15] on the incidence of arteriolosclerosis in cases of hypertension. Fishberg found that 100 per cent of the patients who had hypertension whom he investigated also had renal arteriosclerosis; the corresponding proportion in the investigation of Moritz and Oldt was 97 per cent, and that in the investigation of Bell and Clawson 90 per cent. After we had analyzed their material, however, it was apparent that their results are not comparable with those in this study because of differences in the cases studied. Bell and Clawson and Moritz and Oldt dealt only with cases of severe hypertension, and all of their patients died of the effects of hypertension, for example, from cardiac decompensation, cerebrovascular accidents and renal failure. Although Fishberg did not give the cause of death in all of his cases, it is apparent from the blood pressure readings in his cases that severe hypertension was present. Only 5 of the patients in our study, however, died of the effects of hypertension. The hypertension present in our cases was either not as severe or not as far advanced as in the cases studied by Fishberg, Bell and Clawson and Moritz and Oldt.

The argument might be advanced that the diagnosis of hypertension was incorrect in the 8 cases of pyelonephritic atrophy in our series in which abnormal arteriolar changes had not taken place. On reviewing the records of these cases, however, it was found that reliable and satisfactory blood pressure readings were obtained in 5 of the 8 cases. In these cases, the blood pressure ranged from 158 to 184 mm. systolic and from 86 to 120 mm. diastolic. The mean systolic blood pressure was 170 mm. and the mean diastolic 100. In the 3 cases in which adequate blood pressure readings were not available, the hearts each weighed 50 Gm. or more than the maximal normal for the body weight and the sex as given in the tables of H. L. Smith. The mean weight of these hearts was 423.3 Gm. From these data we are of the opinion that hypertension was present in these cases. In only 1 of these 8 cases, however, was hypertension considered the cause of death. In the other 7 cases hypertension was only an incidental finding. Most of the patients died of neoplastic disease.

The finding of normal renal arterioles and arteries in 8 cases with hypertension suggests that the early stages of hypertension may not be accompanied by renal arteriolosclerosis.

As might be inferred from what has already been said, we were unable to recognize hypertension consistently from the histologic examination of the atrophied kidney or of the nonatrophied opposite kidney. Neither the parenchymal nor the vascular changes were an adequate guide to a diagnosis of hypertension.

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15. Moritz, A. R., and Oldt, M. R.: Am. J. Path. **13**:679, 1937.

SUMMARY AND CONCLUSIONS

The incidence of hypertension was determined in 84 cases of unilateral renal atrophy and 13 cases of unilateral renal hypoplasia. There were 48 cases of pyelonephritic atrophy, 28 of hydronephrotic atrophy and 8 of pyonephrotic atrophy. Death in most of these cases was due to neoplastic disease or infections of various types. Hypertension was a cause of death in only 5 cases. Only in the groups of cases of pyelonephritic atrophy (39.6 per cent) and that of cases of pyonephrotic atrophy (37.5 per cent) was the incidence of hypertension greater than in the control group (29 per cent). The incidence of hypertension was 41.9 per cent for the group of cases of pyelonephritic atrophy in which the atrophied kidney weighed 75 Gm. or less and 35.4 per cent for the group in which the atrophied kidney weighed more than 75 Gm.

In 20 of the 48 cases of pyelonephritic atrophy and in 12 of 25 cases of hydronephrotic atrophy [16] there was some degree of active inflammation in the opposite kidney. Inflammation in the opposite kidney was present more often in cases in which hypertension was a feature than in those in which it was not observed.

The degree of arteriosclerosis in the opposite nonatrophic kidney was generally less severe than that in the atrophied kidney. In 8 of 19 cases of pyelonephritic atrophy associated with hypertension, the blood vessels were considered normal for the age of the patient.

The results, although of questionable statistical significance because of the small number of cases, suggest that unilateral pyelonephritic atrophy is more often associated with hypertension than would be expected on the basis of chance. They also suggest that hypertension is more likely to be present if the degree of atrophy is severe. As abnormal vascular changes had not occurred in the opposite nonatrophic kidney in a number of cases of unilateral renal atrophy associated with hypertension, it is suggested that in many cases in which hypertension is in an early or mild stage it may not be associated with renal arteriolosclerosis.

16. The specimen was not saved in 3 cases.

THE "NERVELESS" SPINAL CORD—A NEW ARTEFACT

HENRY W. EDMONDS, M.D.
BOSTON

The liability of the central nervous system to artefact formation is an established fact. Perhaps in no other organ complex are such bizarre results attributable to postmortem change or to the technic of autopsy. Van Gieson's [1] demonstration of the way in which the anatomic picture of diplomyelia, or congenital duplication of the gray matter of the spinal cord, may be imitated by crushing the cord during its removal from the spinal canal will serve as an instance of such pitfalls. Other examples have been studied by Riedel.[2]

Several years ago, during the performance of a routine autopsy on a newborn infant, Dr. Samuel H. Gray, pathologist to the Jewish Hospital, St. Louis, was surprised to find himself lifting out the entire spinal cord, attached to the medulla and cerebellum. Dr. Gray granted me the privilege of reporting the case.

The head had been opened by the usual Beneke [3] technic, and after removal of the cerebrum the tentorium had been divided by lateral cuts. When the fingers of the operator were inserted under the cerebellum, the entire remaining portion of the central nervous system came away as easily as if there had been no nerves to anchor the cord in the canal. The cord so extracted was found to have been divested of its pia. Its smooth rat-tail-like appearance was similar to that of the spinal cords shown in figure 1. All of the spinal nerve roots emerged from the cord in the ordinary manner, only to be as sharply and as neatly truncated as if they had been clipped off. The cranial nerve roots remained unaltered.

When the spinal canal of the infant was opened anteriorly, the meninges and extrameningeal portions of the nerve roots seemed quite normal. A portion of the meninges so removed was placed in fixative. Unfortunately, this tissue was lost before it could be examined histologically.

From the Laboratory of Pathology, the Boston Lying-in Hospital, and the Department of Obstetrics, Harvard Medical School.

1. Van Gieson, I.: New York M. J. **56**:337, 365 and 421, 1892.
2. Riedel, I.: Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:330, 1928.
3. Beneke, R.: München. med. Wchnschr. **57**:2125, 1910.

Blocks were taken from many levels of this curious cord and were sectioned serially by Dr. James L. O'Leary, of the department of cytology, Washington University School of Medicine, St. Louis. Dr. O'Leary

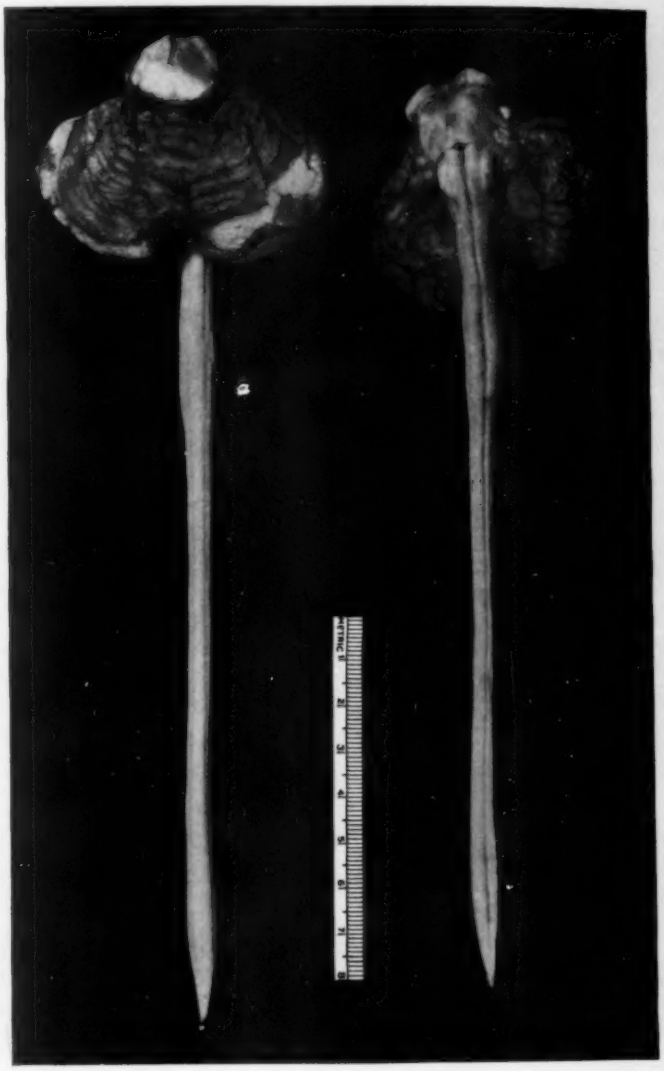

Fig. 1.—Two "nerveless" spinal cords removed by the technic described. The posterior and anterior aspects are shown on the left and right, respectively.

gave me the privilege of reporting his studies of these sections. Not the slightest morphologic abnormality could be detected in either the cord or the adherent stumps of nerve roots.

The other findings in the case seemed irrelevant. The child had been well formed and fully developed. The heart had beat for several minutes, although neither respiration nor voluntary movements had occurred. It was thought that the case might conceivably be one of an anomaly of the nervous system, the nerves having developed outside the meninges, apart from the cord.

There are obvious shortcomings to such a hypothesis. Such a belief would be out of harmony with all known facts of embryology. The anterior roots extend from ganglion cells within the cord, while from the posterior root ganglions arise the long fibers of the posterior tracts of the cord.

An alternative explanation, that the condition might be one of congenital amputation, analogous to that in which a supernumerary digit occasionally falls away by atrophy of its pedicle, was rejected as improbable since the stumps of the nerve roots showed no tissue changes consonant with such a hypothesis (fig. 2 *A*). No parallel to this case could be found in the literature. The data were laid aside as an enigma.

Interest was revived in 1939 when the spinal cords of two other infants were removed in the same remarkable manner in autopsies by Dr. Walter J. Siebert, pathologist to the DePaul Hospital, St. Louis. The cases are reported with Dr. Siebert's permission.

The latter 2 cases were unrelated and occurred in the space of a few months. One of the babies was stillborn; the other had lived several hours. In each case the central nervous system was found histologically normal. The autopsies were restricted to the head (a question of intracranial hemorrhage), so that it was not possible to obtain portions of the spinal meninges or the nerves.

The leading clue was found while an autopsy was being done on a newborn infant. An attempt was made to section, with a blunt knife, a part of the spinal cord that had been removed by the ordinary anterior approach to the spinal canal. This piece of cord, still enveloped in its meninges, had been placed on the table. The pressure of the knife crushed through the cord but failed to sever the meninges. This served to force out the enclosed segment of the cord much as similar pressure will force paste from the orifice of a metal tube. The pieces of cord so stripped of their meninges were in all respects similar to the "nerveless" spinal cord that had originally attracted attention. Here was such a cord produced by accident. It seemed evident that "nerveless" removal of a spinal cord must depend on such a mechanism, operative while the cord is still in the spinal canal.

Such compression may be exerted by flexing the body of an infant as sharply as possible. Experiment has shown that this is best accomplished

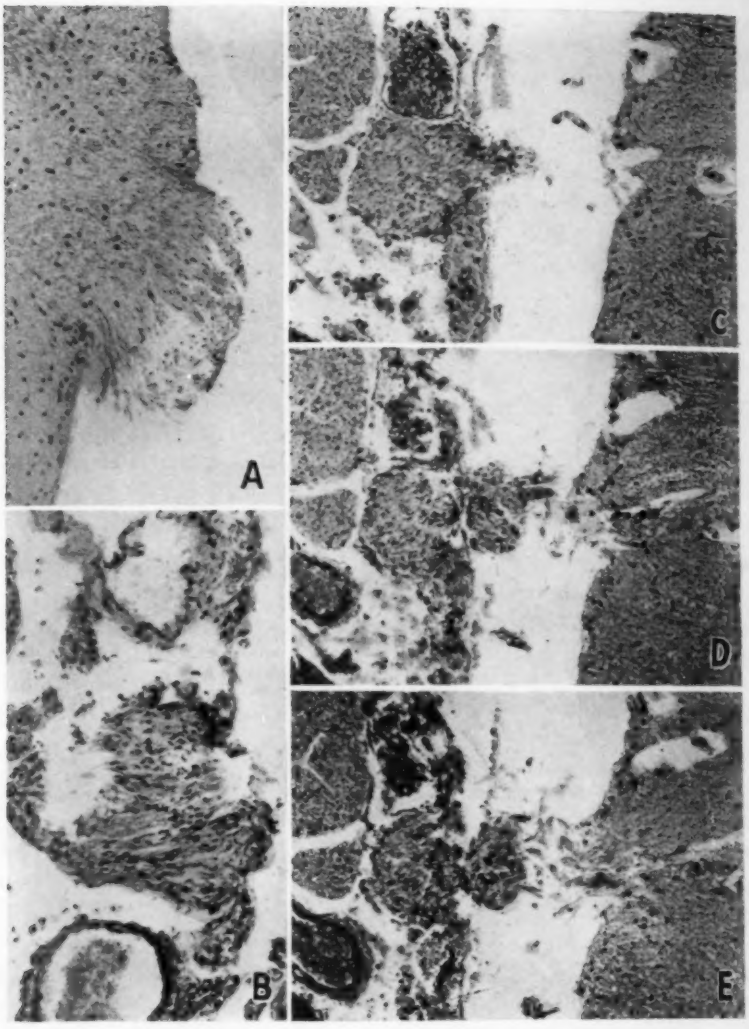

Fig. 2.—Photomicrographs, × 100. *A* and *B*, sections stained with hematoxylin and eosin; *C*, *D* and *E*, sections stained with phosphotungstic acid-hematoxylin. *A* shows a dorsal root emerging from the cord, the end of which is frayed slightly as a result of "nerveless" extraction; *B*, extrapial end of a nerve root, still held in its pial cuff (meninges removed by anterior approach after "nerveless" extraction of the cord); *C*, *D* and *E*, serial sections 42 microns apart, showing passage of a dorsal root through the pia (spinal cord to right, extrapial portions of the nerve roots to left). (The cord was removed by the ordinary method and sectioned without removal from the meninges.)

by placing the cadaver in a sitting position, subsequent to opening the head, and by putting pressure on the shoulders. The entire brain and spinal cord can then be lifted out, once the tentorium has been severed to free the cerebellum and once the cranial nerves have been cut. The maneuver is facilitated if the pia is gently stripped back from the lower part of the medulla and if the shoulder pressure is maintained during the delivery of the cord through the foramen magnum.

Since its discovery, this process has been employed with varying success in a number of autopsies on newborn infants. Specimens as complete as the two shown in figure 1 may be obtained in almost any full term nonmacerated infant, stillborn or not. The central nervous system of the premature or of the macerated infant lacks sufficient tensile strength to withstand the slight strain of the pull. In a child past the first few weeks of life the nerve roots have become too strong to be ruptured by the procedure utilized. It has not been possible to correlate the observed age differences in liability of spinal cords to "nerveless" removal with differences in the histologic pattern of the nerve roots or meninges. There is no significant change in myelination of the nerve roots at or near birth (Langworthy [4]), and no appreciable alteration in the connective tissue of these structures. Within ordinary limits, time elapsing between death and performance of autopsy has seemed to have no effect on the procedure.

The normal anatomy of the nerve root and of the pia affords explanation of the mechanism involved. As demonstrated in figure 2 *C, D* and *E* (ordinary removal of cord), the outer pia is applied about the body of the emergent nerve root in the form of a tight collar. A few of the collagen fibers of pia seem even to penetrate the substance of the nerve, so that a section through the junction reminds one of the passage of the optic nerve through the lamina cribrosa of the sclera. As a result of the dehydration inherent in the preparation of tissues, the spinal cord shrinks inside its pial investment. The cuff of outer pia just described holds the nerve root so that it tears away at its weakest point—between the site of emergence from the cord and the site of penetration of the outer pia. This mechanism is quite analogous to that which is effective when the spinal column of a cadaver is flexed with the cord in situ. In the latter instance, the cord is forced slightly toward the foramen magnum, while the meninges serve to anchor the nerves to the wall of the spinal canal. The nerves snap at the point of least resistance—the site of emergence from the cord proper. The microscopic appearance of the two ends of nerves so severed (fig. 2 *A* and *B*) is in accord with such an explanation.

4. Langworthy, O. R.: Contrib. Embryol. **24**:1, 1933.

SUMMARY

The extraction of the intact spinal cord via the foramen magnum, first observed accidentally and later repeated at will, may be accomplished in almost any mature nonmacerated newborn infant. The requisite maneuver, executed by sharply flexing the spine of the cadaver while lifting the brain from the opened head, is explained on the basis of the countertraction exerted on the emergent nerve root by the cuff of pia that normally invests it. The "nerveless" condition of a cord so removed is thus a simple artefact of autopsy technic.

Case Reports

PECULIAR NECROSIS OF THE LIVER IN A CASE OF HEMOCHROMATOSIS

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The purpose of this paper is to describe necrosis of the liver in a case of hemochromatosis, the lesion appearing grossly very much like carcinomatosis on the basis of cirrhosis.

REPORT OF CASE

The patient, a 59 year old white man, was without complaints until July 1, 1940, when he vomited bright red blood. Again, August 22 and 23, he had marked hematemesis, for which he was hospitalized with a blood pressure of 90 systolic and 68 diastolic. The urine at this time gave a reduction resulting in a green color with Benedict's solution. The blood shortly after admission revealed a hemoglobin content of 60 per cent and 2,840,000 red corpuscles. The Kahn test was negative. After supportive treatment the patient was put on a diet for ulcer and discharged. He was readmitted Jan. 21, 1941 in shock with a blood pressure of 84 systolic and 62 diastolic, bleeding from the stomach, vomiting and passing blood by rectum. The urine at this time was negative for sugar. In spite of several blood transfusions and intravenous injections of dextrose, he continued to bleed and died on January 26.

His father died of heart trouble; otherwise the family history was not relative. The patient stated that he had never had a venereal disease. He had consumed very little alcoholic liquor.

There was no pigmentation of the skin; the chest was normal; there was tenderness in the lower quadrants of the abdomen and in the back; the extremities and the genitalia were essentially normal. The temperature at the time of both admissions was 96.4 F. (mouth) and during his hospital stays ranged between normal and 100 F. Terminally it was 100 F. (axillary).

Autopsy.—The postmortem examination made immediately after death, revealed: pigmentary cirrhosis of the liver with multiple necroses; hemosiderosis, atrophy and lipomatosis of the pancreas; hemosiderosis of the portal and peripancreatic lymph nodes and of the lymph nodes at the hilus of the spleen; chronic splenic tumor; varices in the lower part of the esophagus and at the cardia, with rupture of one varix, and about 1 liter of blood in the stomach; secondary anemia; diminution of the lipoid content of the adrenals; atelectasis of the lower lobes of both lungs; old adhesions of the pleura and of the peritoneum on the right.

The cadaver was that of a white man, 179 cm. in length, well developed and well nourished. The eyes and the mucous membranes were normal. There was no increased pigmentation of the skin. There was an old, tough adhesive pleuritis surrounding the lower lobe of the right lung. There was atelectasis of the lower lobes of both lungs. The heart did not show pathologic changes. The coronary arteries were slightly sclerotic but patent. The aorta presented a moderate number of atheromatous plaques. The esophagus contained several markedly enlarged veins lying parallel and running lengthwise of the esophagus, causing the mucosa

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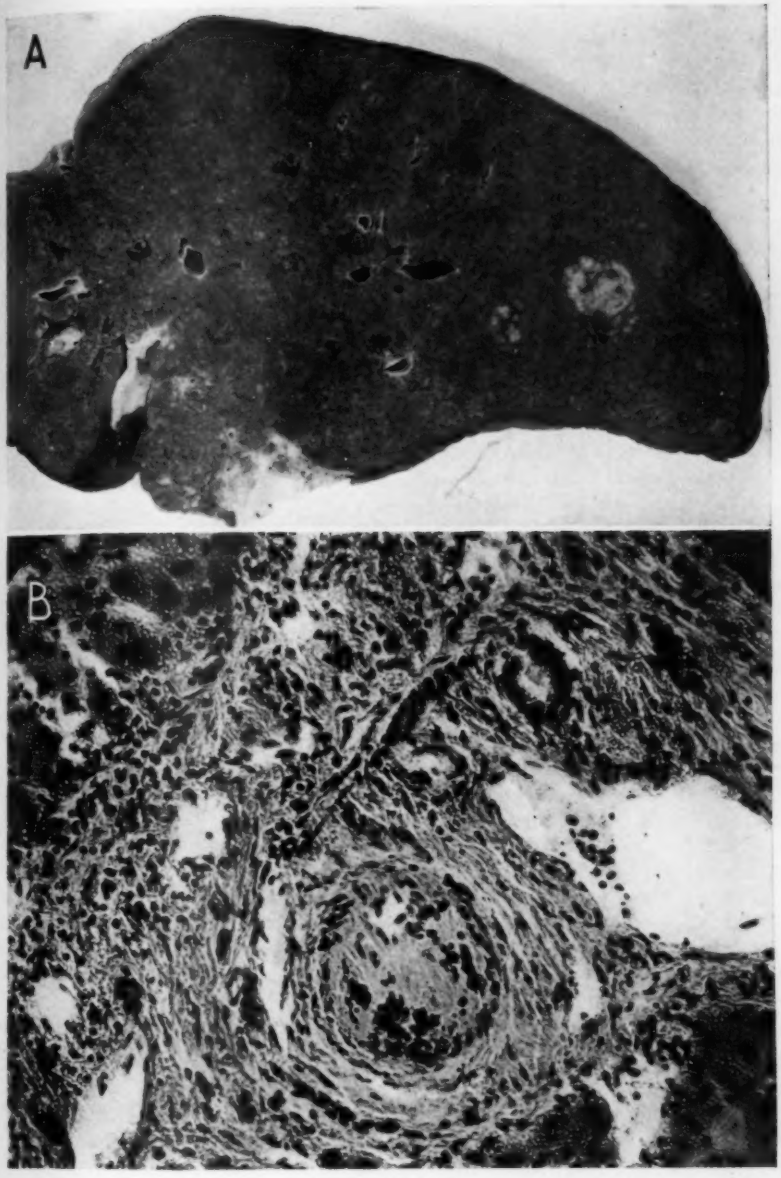
to bulge. About 1 cm. proximal to the cardiac orifice of the stomach there was an opening through the mucosa over one of these vessels, with a slight pinkish reaction around it, through which blood could be expressed. It was about 1 mm. in diameter. The stomach was dilated and contained a huge clot of blood, amounting roughly to 1 liter. The remainder of the intestinal tract was filled with liquid feces mixed with black blood.

The liver weighed 1,500 Gm. and was hard, its surface being rough and finely puckered. The color was rusty brown, and the normal markings were absent. The liver showed a transformation of its structure typical of atrophic cirrhosis, with a great many new-formed pseudoacini, round in shape and about the size of a peppercorn. The fibrous tissue between these pseudoacini appeared increased and brown. In many places the cut surface showed round, yellowish white, well circumscribed areas, soft in consistency and of medullar appearance. The size of these foci, which most resembled a malignant medullar tumor, varied from that of a peppercorn to that of a small cherry (*A* in figure).

The pancreas was markedly atrophic and also rusty brown. The spleen was large, weighing 850 Gm., and on section was mottled light and dark red. It was firm; the pulp could not be wiped off on the knife blade. The kidneys were of normal size; the capsules stripped easily; the cut surface was anemic, but the markings were normal. The ureters and the bladder were normal. The adrenals were somewhat smaller than normal and showed a marked diminution in their lipoid content.

Microscopic Description.—The liver presented the picture of cirrhosis with far advanced transformation of its structure, showing round pseudoacini, which were partly well circumscribed by proliferated fibrous tissue, partly coalesced with neighboring acini. While for the most part the liver parenchyma consisted of new-formed acini, old atrophic liver cell cords were demonstrable in many places among the regenerated areas. Especially in these parts, but also in the new-formed acini, particularly in their periphery, there was an enormous amount of hemosiderin. A slight amount of iron pigment was contained in some of the Kupffer cells. The stroma surrounding the pseudoacini or parts of them was abundantly proliferated and infiltrated by many lymphocytes. It showed numerous small, mostly atrophic pseudobiliary canaliculi and a huge but variable amount of iron pigment.

As far as the described picture was concerned, the liver exhibited the common features of pigmentary cirrhosis. In many places, however, some of the pseudoacini were involved by extensive necrosis that frequently occupied almost the whole acinus, leaving undestroyed only a small rim of the periphery. For the most part, some remnants of structure were preserved within the area of necrosis, and liver cell cords, although without nuclei, were frequently discernible. In other acini the central parts of the areas of necrosis were entirely destroyed, showing a great amount of dark blue-stained debris made up of broken nuclei. Between the necrosis and the preserved periphery there was a narrow, or sometimes a wide, zone consisting of stroma without liver cells but containing a great number of phagocytes, the cytoplasm of which was heavily loaded with brown iron pigment. Sections stained with sudan and hematoxylin showed a slight amount of lipoid within the areas of necrosis, the lipoid consisting of tiny fat droplets. The rest of the liver parenchyma revealed only scattered small areas of fat-containing liver cells. In sections stained with Best's carmine there were a few irregularly distributed small liver cell groups containing glycogen. In the thickened portobiliary connective tissue there were demonstrable occasional structures that con-



A, cross section through the liver, showing the markings of atrophic cirrhosis with well defined tumor-like necrotic areas. *B*, a small branch of the hepatic artery under high power magnification, showing almost complete obstruction of the lumen and deposition of iron pigment in the wall.

sisted of clusters of a few nuclei, possibly those of endothelium, surrounded by hyalinized fibrous tissue, these structures suggesting obliterated vessel walls. If one traced these structures in serial sections, it was possible to demonstrate that they were virtually small vessels with closed lumens. Somewhat larger arterioles had lumens, but these were markedly narrowed, and the vessel walls showed mostly eccentric thickenings, due not only to proliferation and hyalinization of fibrous tissue but also to proliferation of the elastic membranes. These thickenings sometimes contained deposits of hemosiderin, which are found only occasionally in the walls of hepatic vessels in hemochromatosis (*B* in figure).

Only the small and smallest arteries were involved by the lesion described; larger vessels did not have striking lesions. The hepatic artery in its extrahepatic course showed only moderate atherosclerosis, with thickening of the intima and fibrosis and mucoid degeneration of the media but without noteworthy narrowing of the lumen.

The portal vein seemed normal, but in the splenic vein there was a mural thrombus, organized at its base, with a more recent reddish white stratified part superimposed. The vessel wall appeared thickened, and the lumen narrowed, owing to the mural thrombosis.

The pancreas showed a moderate degree of fibrous atrophy with lipomatosis and huge deposits of hemosiderin. Although the Langhans islands were not counted, a general survey of the sections disclosed a marked diminution in their numbers; some of the still remaining ones were atrophic, and some were enlarged, apparently owing to compensatory hypertrophy.

The peripancreatic lymph nodes exhibited definite fibrosis with intensive hemosiderosis.

There was hyperplasia of the red pulp of the spleen with increase in the number of reticular fibers, while the follicles were definitely atrophic and the follicle artery was thickened and hyalinized, with narrowed lumen. Staining for iron showed a slight amount of hemosiderin in the red pulp and a larger amount accumulated in spots at the border of some of the trabeculae.

There was a striking paucity of lipoid in the adrenal cortex. The reticular zone was markedly pigmented by lipofuscin. By the Turnbull blue method, hemosiderin was disclosed within small areas of the glomerular zone and, in small amounts, in the medulla, being found in the cytoplasm of the chromaffin cells.

There was slight arteriosclerotic atrophy of the kidneys, together with traces of hemosiderin in the interstices.

The section of lung tissue examined showed a partly hemorrhagic serous effusion in the alveoli. Numerous phagocytic elements within this effusion were loaded with hemosiderin, while small amounts of hemosiderin together with coal dust pigment were to be found here and there in the interstitial tissue around the vessels.

The cardiac glands of the esophagus had deposits of hemosiderin in their epithelium.

A part of the fundic glands of the stomach contained a slight amount of iron pigment in their basal portion, whereas in the basal portion of the glands in the antrum of the pylorus was a large amount of pigment.

COMMENT

This was a case of pigmentary cirrhosis. The hemosiderosis of the liver, pancreas and abdominal lymph nodes was extensive, while that of the spleen, adrenals, lung, stomach and other organs was less marked. Hemofuscin was not demonstrated in smooth muscle fibers or other

tissues. Sugar was present in the urine. Despite the fact that some of the symptoms were missing—for example, the pigmentation of the skin—the case is to be considered one of hemochromatosis both clinically and pathologically, although we think it would better be denoted as "forme fruste." Unfortunately, the testes were not examined, so that statements concerning the sexual status of the patient are not complete. The patient died of exsanguination from a ruptured varix in the esophagus, an event observed in about 5.5 per cent of the cases (Sheldon [1]).

In extensive studies of the literature only 1 case was found in which the lesions of the liver possibly had a partial resemblance to those found in our case.[2] In that case, described by Oestrreich, there were an initial cirrhosis, moderate jaundice, and fibrosis of the pancreas, together with fat necrosis in the mesentery and omentum. There was subcapsular necrosis in the liver, thought to be due to a pancreatic ferment carried to the liver. These conditions were not present in our case. On the other hand, that case was not one of hemochromatosis.

In trying to find the cause of the hepatic lesions, we first studied the blood supply to the new-formed acini for evidence of atherosclerosis, endarteritis, embolism or thrombosis.

Other possible causes might be sought in toxins with necrotizing action on the liver parenchyma or in necrosis due to reflux of pancreatic juice into the liver, as the case mentioned before seemed to show. These conditions could, of course, not be proved morphologically. Against the hypothetic assumption of toxins without any other agent being the cause of the necrosis spoke the anatomic appearance of the necrotic foci, characterized by irregularity of distribution and size. Areas of toxic necrosis of the liver are more regular in distribution and more equal in size. Reflux of pancreatic juice as a cause of necrosis has been described several times but was not seriously considered in our case, because certain conditions, such as cholelithiasis and hemorrhagic pancreatitis,[3] which accompany this type of hepatic necrosis were missing. A test for lipase in the bile as evidence that pancreatic juice had entered the liver was not done in our case.

By means of serial sections, lesions were found in the small branches of the hepatic artery which morphologically corresponded to atherosclerosis and resulted in complete or almost complete closure of the lumens. These lesions, which were found in close anatomic relationship to the necrotic areas, at least indicated a great impairment of the blood supply to the new-formed liver acini.

Atherosclerosis is such a frequent condition, although not so frequent in the liver as in many other organs, that it would not be understandable why necrosis should not occur much more frequently in cirrhotic livers if arteriosclerosis alone were able to produce it. Therefore, some additional agents must be considered which together with the impairment of the blood supply might have exerted their deadly action on the liver parenchyma. Here we could think of some toxins, perhaps the same

1. Sheldon, J. H.: Haemochromatosis, London, Oxford University Press, 1935, p. 34.

2. Oestrreich: Zentralbl. f. allg. Path. u. path. Anat. **19**:145, 1908.

3. Schiller, W.: Surg., Gynec. & Obst. **72**:70, 1941.

ones that produced the hemosiderosis, as having damaged the newformed liver parenchyma and lowered its resistance, so that it succumbed more easily to the ischemia resulting from the sclerosis of the blood vessels.

We also have to consider the partial thrombosis of the splenic vein. Tiny emboli brought to small branches of the portal vein, together with the impaired blood supply through the obstructed hepatic arterioles, could have played a part in the genesis of the necrotic areas. Since in a careful examination no emboli or thrombi were found in branches of the portal vein, this idea was discarded.

SUMMARY

In a case of hemochromatosis necrotic foci were found in the cirrhotic liver which grossly simulated a malignant tumor. Severe atherosclerotic lesions in small branches of the hepatic artery, probably together with other undisclosed factors, played an important part in the genesis of these peculiar necroses.

MYXOMA OF THE HEART

RICHARD DEXTER, M.D., AND JOHN L. WORK, M.D., CLEVELAND

That primary myxoma of the heart occurs less frequently than the total number of cases reported in the literature would indicate is suggested by the fact that but few observers have described more than a single case of their own. At any rate, we believe that the disease is still sufficiently uncommon and still sufficiently interesting from the clinical and pathologic points of view to justify a description of the following case.

REPORT OF A CASE

A married white woman, 53 years of age, was admitted to the St. Alexis Hospital Nov. 7, 1940 for study of a depressed mental condition, which had become apparent about one month before admission. She complained of dizziness and loss of memory. The only other complaints were: increasing shortness of breath on exertion, which had been noticed for about a year, and episodes of cardiac palpitation and rapid pulse. These symptoms had not been severe enough to cause her to interrupt her usual activities. The personal history and the family history were noncontributory. There was no history of rheumatic fever or of other infection.

The patient was a well developed and well nourished woman, mentally depressed and somewhat disoriented. The temperature was 98.6 F., the pulse rate was 100 per minute and the respiratory rate 20. The color was good. The pupils reacted to light and in accommodation, and the ears and buccal cavity were normal. The thyroid was not enlarged. The chest was well formed, and expansion was equal. The lungs showed no abnormalities. The apex impulse was palpable just outside of the left midclavicular line; no thrills were felt. The left border of cardiac dulness was 2 cm. to the left of the midclavicular line, but there was no enlargement either to the right or upward. A loud systolic murmur was audible at the apex of the heart and was transmitted to the axilla. The neurologic findings were normal except for rotary nystagmus, and the neuropsychiatric consultant summarized his report as follows: "A depression is noted which causes apparent memory defects, but the latter are due to psychomotor retardation. The neurologic findings suggest organic factors, but the type of mental reaction is not that of the organic psychoses."

The hemoglobin content of the blood was 9.0 Gm. (Sahli), and the erythrocyte count was 3,900,000; there were 6,600 leukocytes per cubic millimeter of blood, and the differential count was normal. The urine was acid, had a specific gravity of 1.009 and gave negative reactions for albumin and sugar. The Pandy and Kline tests of the spinal fluid were negative, and the mastic curve was normal. A stereoscopic roentgen examination of the skull showed no abnormalities.

With administration of thiamine hydrochloride and nicotinic acid the mental condition improved, and the patient was discharged thirteen days after admission

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with a diagnosis of menopausal syndrome and rheumatic heart disease, inactive, with cardiac hypertrophy and mitral incompetence.

She was readmitted Dec. 21, 1940, thirty days after discharge, with the history that she had been well until one week before, at which time a cough developed and she noticed increasing shortness of breath. The latter became severe, and she had pain in her left shoulder and in the lower part of the left side of her chest.

Examination at this time revealed pallor, cyanosis and orthopnea, with shallow respirations occurring at the rate of 48 per minute. The veins of the neck were prominent. The left side of the chest moved less than the right. Over the base of the left lung there was marked dulness with numerous consonating rales, tubular breath sounds and increased tactile fremitus. The apex impulse was faint and diffuse, and the left border of cardiac dulness was 5 cm. beyond the midclavicular line. The sounds were of fair quality and regular, and the rate was 120 beats per minute. The first sound at the apex had a ringing quality, was preceded by a short crescendo murmur and was followed by a short, soft systolic murmur. The pulmonic second sound was increased. The radial pulse was soft and regular, with a rate the same as that of the heart. The blood pressure was 78 systolic and 55 diastolic. The liver was tender to palpation but was not demonstrably enlarged. The temperature was 102 F.

The hemoglobin determination and the erythrocyte count gave values approximately equal to those obtained at the time of the first admission. The leukocyte count was 12,500, and the sedimentation rate, determined by the Westergren method, was 63 mm. The urine contained albumin, 1 plus, numerous leukocytes and fine and coarse granular casts. Electrocardiograms showed sinus rhythm, right preponderance, low voltage QRS and small T waves or absence of T waves in all leads. The circulation time for decholin was twenty-five seconds and that for ether eight seconds. A roentgen examination of the chest showed decreased aeration at the base of the right lung and a small amount of fluid at the base of the left pleural cavity. The heart was enlarged in the region of the left ventricle and in that of the left auricle, indicating to the roentgenologist the presence of mitral stenosis.

The patient became rapidly worse. The temperature rose, reaching 106 F., with a pulse rate of 130 and a respiratory rate of 60 per minute, on the third hospital day. She died early on the fourth day after admission. The clinical diagnosis was bronchopneumonia, rheumatic heart disease with mitral stenosis and insufficiency, and cardiac dilatation.

Autopsy (four hours after death).—The body was that of a small but well developed and well nourished asthenic white woman appearing to be about the stated age of 53 years. The veins of the head, neck and shoulders were distended, and there was marked telangectasia of the face. There was moderate edema of both lower extremities, as well as mild edema of the right hand and distal half of the forearm. There was slight clubbing of the fingers.

The heart weighed 350 Gm. and was dilated, particularly on the right side. The epicardium was normal except for a single so-called "milk plaque" and slight thickening along the coronary sulcus, where there were a few delicate adhesions. The myocardium was normal. The foramen ovale was anatomically closed. Arising from the left side of the atrial septum and from the inferior border of the valve of the foramen ovale, which was fused to the septum except for a short distance along its anterior margin, there was a large pear-shaped lobulated mass which

measured 4.5 by 4.2 by 3.5 cm. This was suspended from the septum by a broad pedicle, on which it could be rotated in all planes. The small end hung into the mitral orifice, and its tip extended approximately 2 cm. below the valve ring (fig. 1). The tumor was soft but resilient, only slightly friable and mottled translucent gray and dark reddish brown. Its gross structure was homogeneous and gelatinous except at the base, whence delicate yellow fibers radiated into the substance of the tumor. The endocardium lining the left atrium was thickened and presented delicate ridges, which were most numerous beneath the base of the tumor. The tricuspid, pulmonic, mitral and aortic valve rings, respectively,

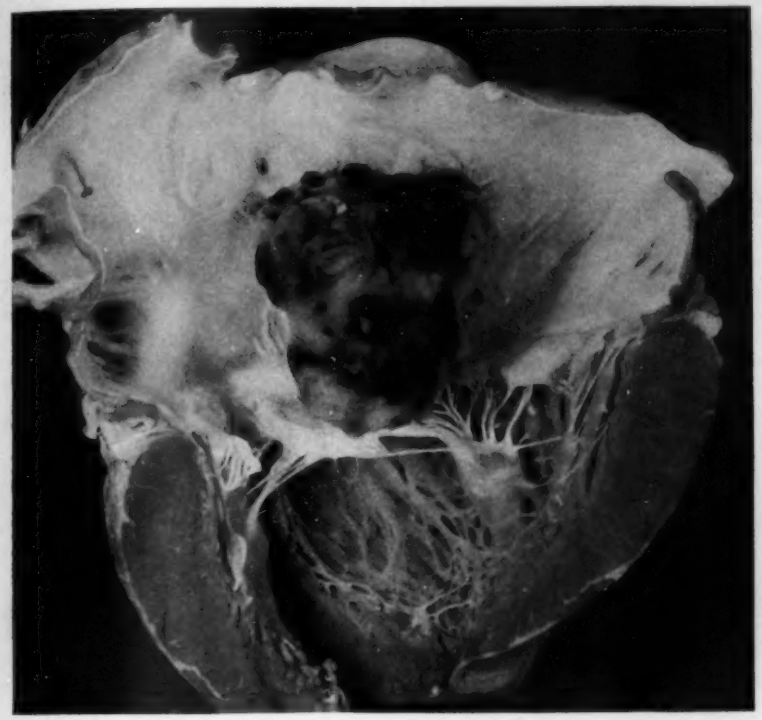

Fig. 1.—Photograph of the heart, showing the tumor hanging through the mitral orifice.

measured 11.3, 6.8, 9.5 and 6.0 cm. in circumference. There were slight shortening and marginal thickening of both mitral leaflets, and the chordae tendineae attached to them were mildly thickened, shortened and occasionally fused. The aortic leaflets were slightly thickened at the base of their attachment and showed slight firm fibrous submarginal adhesions in the commissures. The tricuspid and pulmonic valves were normal. There was no significant arteriosclerosis of the coronary arteries, of the aorta or of its branches, and no emboli were found.

Microscopic preparations of the tumor (fig. 2) showed it to be composed of a loose network of cells supported in an abundant homogeneous, faintly eosinophilic matrix. The cells were spindle shaped, stellate or pyramidal, with delicate

anastomosing fibrillary processes frequently lost in the intercellular substance. A small proportion of the cells were round or oval, with distinct cell membranes, and there were scattered multinucleated forms with three to ten compact or finely vesicular nuclei. The cells were condensed at the surface of the tumor and frequently grouped about capillaries and blood spaces, where they occasionally formed radial palisades. There was a fine network of delicate elastic fibers throughout the tumor, and the matrix stained a deep pink with mucicarmine. There was patchy extravasation of erythrocytes, and numerous hemosiderin-containing phagocytes were present in the stalk. Selected sections through the pedicle showed it to originate from well vascularized subendothelial connective tissue without interruption of the medial elastic fiber network of the endocardium. Sections

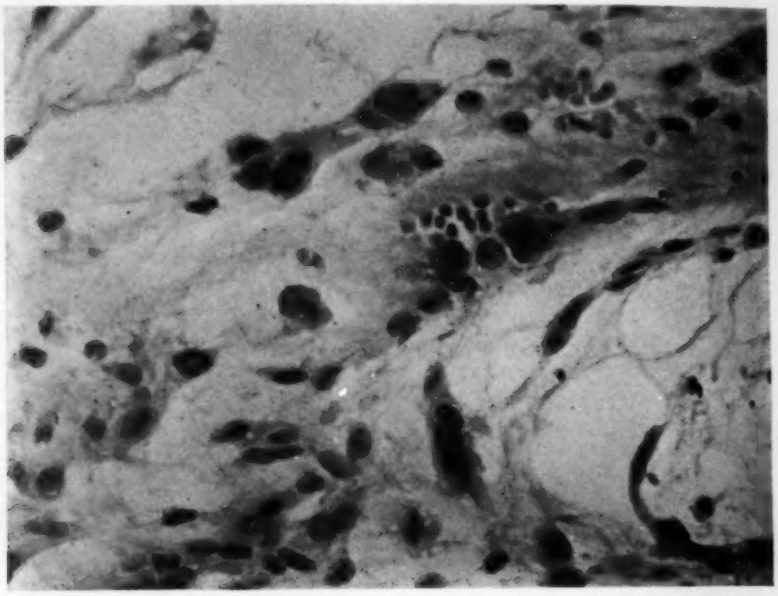

Fig. 2.—Photomicrograph of the tumor; hematoxylin-eosin; × 700.

through the ventricular walls and through the posterior mitral leaflet showed no evidence of active rheumatic disease.

There was severe edema of the lungs with moderate passive hyperemia of the lungs and abdominal viscera, which sections of the liver and spleen indicated had been present for a considerable period. There was bilateral hydrothorax with approximately 750 and 500 cc. in the right and left cavities, respectively. Small branches of the pulmonary artery in both lungs were plugged with thrombi, and there was a group of small infarcts in the lower lobe of the left lung. There were also a few small infarcts in the spleen and both kidneys, some of which were partially organized. No tumor was found in these lesions.

The incidental findings included a number of congenital anomalies: incomplete rotation and ascent of the right kidney, an accessory right renal artery, Meckel's diverticulum and incomplete fixation of the cecum.

The head and spinal cord were not examined.

The anatomic diagnosis was: myxoma of the heart, arising from the left side of the atrial septum, with prolapse into the orifice of the mitral valve; dilatation of the heart, predominantly right sided; edema of the lungs; passive hyperemia of the viscera.

COMMENT

A question has been raised as to whether a lesion of this sort in the heart is a true neoplasm or a new growth not truly neoplastic originating in granulation tissue. In this case the presence of lesions indicative of extinct rheumatic cardiac disease is clearcut. The fact that in rheumatic disease the posterior and the septal wall of the left atrium are frequently involved may be of significance. It is thus conceivable that inflammation of a rheumatic character operating in this situation left a residuum on which granulation tissue developed, ultimately producing the tumor mass. It is unfortunate that in many of the case reports the descriptions are not adequate in the light of our comparatively recent appreciation of the minor manifestations to justify the exclusion of extinct rheumatic carditis. In the future it may well be that the association of rheumatic disease, extinct or chronic, with myxoma of the heart will be found more frequently.

SUMMARY

A case of primary myxoma of the heart has been described. The condition was mistakenly diagnosed as rheumatic heart disease because the size and position of the tumor caused physical signs and a cardiac silhouette in the roentgen film typical of long-standing stenosis of the mitral valve. The tumor originated from the subendothelial connective tissue of the endocardium of the left side of the atrial septum and had prolapsed into the orifice of the mitral valve, where doubtless it acted as a ball valve preventing the free flow of blood from the left atrium into the ventricle. The scars of previous rheumatic carditis were present, but the degree of involvement was not considered sufficient in itself to have impaired the function of the heart or to have given physical signs of involvement of the valves. The tumor had the histologic structure of true myxoma.

General Reviews

MYOCARDITIS

A GENERAL REVIEW, WITH AN ANALYSIS OF TWO HUNDRED AND FORTY CASES

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The incidence of the diagnosis of myocarditis has undergone more changes than perhaps the incidence of any other diagnosis. Not so many years ago almost every elderly patient who died had "chronic myocarditis" written on his death certificate. In those days any lesion in the myocardium, whether primarily vascular, degenerative or inflammatory, was designated as "chronic myocarditis." When the various city and state health departments were hesitant in accepting "chronic myocarditis" as the cause of death and when finally the morphologist had convinced the clinicians of the advisability of using the term only when there was evidence of a primary true inflammation of the myocardium, myocarditis became a rare diagnosis. Though there are still many clinicians who use the term "chronic myocarditis" to denote the results of primary vascular disease, the term is used less and less. Furthermore, in the attempt to diagnose heart disease more accurately, White stated, the term "myocarditis" is being wisely abandoned in large part. It must be remembered, nevertheless, he continued, that such a condition as myocarditis occurs. On the other hand, there are clinicians who emphasize that myocarditis in the true sense of the word has not been correctly appraised in regard to its importance and frequency. They stress the fact that true myocarditis is a common disease and quite often remains unrecognized. The discrepancies in these two views are apparently the result of the difficulties in recognizing acute myocarditis clinically. This is borne out clearly by the statement of White that "it can be diagnosed clinically only by the realization of the frequency of mild to moderate involvement of the myocardium in these infections (diphtheria, etc.) and in a few cases circumstantially by the finding of acute heart block, abnormal electrocardiograms, or acute cardiac dilatation without definite valvular lesions, coronary disease, or hypertension to account for the dilatation."

Scherf and Boyd stressed the fact that the frequency of myocarditis and the difficulty of its diagnosis are generally appreciated only after electrocardiographic studies of clinical material have been conducted

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regularly. Moreover, these authors held that electrocardiographic alterations are not evident in all cases nor continually in those in which the condition is demonstrable; they develop when foci of inflammation exist at definite places (for example, in the bundle of His, in the atrioventricular node or in one of the major conduction branches) or when larger foci are located in the muscle substance. These authors stated that since new foci of inflammation constantly light up and vanish, the alterations in the electrocardiograms (conduction disturbances, broadened QRS complexes, abnormal T waves) may be present today and gone tomorrow. By regular daily electrocardiographic study these observers were enabled to state that in every case of endocarditis there is an accompaniment of myocarditis and that in every case of acute rheumatic fever foci of inflammation are simultaneously demonstrable in the heart muscle. Myocarditis is only one localization of the "rheumatic infection."

Naturally, whether these fleeting electrocardiographic changes are brought about by inflammatory lesions still remains to be seen, since there is very little control autopsy material on hand either to corroborate or to refute the speculations about them.

This controversy is clearly stated by Rothschild who in a rather philosophic vein said:

> With the development of newer physiological methods of study, such as the electrocardiogram, simple methods of studying the gaseous exchange, vital capacity determinations, blood volume methods, and circulatory time determinations, our concepts broadened. "Circulatory failure" superseded "heart failure" as the generic term. Disturbances of function were found to occur without demonstrable morphologic change. Clinicians became more discerning, and attempted to analyze more closely just what part of the circulatory mechanism was at fault. The diagnosis of myocarditis became less frequent and prophetically will become even less frequent.

Also Šikl did not escape the prevailing opinion against the importance of anatomically demonstrable heart changes versus clinical findings. He emphasized that it cannot be denied that lately rather strong skepticism has been prevalent as to the range of the anatomic method of investigation and that this may be said with particular reference to the pathologic conditions of the myocardium.

Thomas Lewis was particularly outspoken in stating that the use of the term "myocarditis" is scarcely justified clinically except in relation to rheumatism, and in this relation the term "carditis" is sounder. The description of myocarditis, acute or chronic, as a separate disease with its special symptoms and signs needlessly complicates a general description of cardiac disease, which it is essential should remain simple. Though not referring to myocarditis per se but to "fatty heart," he further ventured:

> If a man dies suddenly in the street, a court is required to find the reason, and if nothing else is forthcoming, "fatty heart" by usage proves convenient and acceptable.

The enquiry may not rest upon the answer "death from natural causes" unless an anatomical basis for death is found. There is evidence that the ventricles of elderly people, and especially those presenting disease, are prone to fibrillate. This fatal fibrillation is an event in living muscle; it leaves no message written upon the dead heart. The conception that correlates fatty heart and sudden death may be useful, and therefore still justifiable, in forensic practice, but while fatty heart is usually unrecognizable in the living and its prognostic significance is uncertain, the conception can find no place in clinical diagnosis.

Christian recently discussed myocarditis. He said:

If by acute myocarditis is meant an actual inflammatory process of the myocardium with infiltration by polymorphonuclear leukocytes, this is a rare condition and consequently of minor clinical importance. On the other hand, if by acute myocarditis is meant the circulatory disturbances, with or without evidence of degeneration of the muscle fibers or cellular infiltration between them, associated with acute infectious diseases, it is a frequent occurrence.

In going over the records in 240 cases in which at autopsy the diagnosis of myocarditis (nonsyphilitic) was made and in many of which death was attributed to the myocardial lesion, it is distressing to find in how few instances the clinical diagnosis of myocarditis was made. Inadvertently one is reminded of Rothschild's prophetic remark that the diagnosis of myocarditis will become even less frequent.

It is apparently true that the diagnosis of myocarditis is difficult to make. Yet it is clear that by ignoring the anatomic finding and substituting "fatal fibrillation" and "circulatory failure" for these changes the clinician, though impressed by the general appearance of the patient, goes further and further away from an anatomic picture the clinical equivalent of which today still seems to be not fully understood. And perhaps because of the skepticism of the clinician, the pathologist also, who could not correlate the anatomic and the clinical picture, has lost interest in myocarditis. This was clearly recognized by Edens, who named myocarditis the "step-child" of pathology.

Another reason for the marked discrepancies between the anatomic and the clinical diagnosis of myocarditis and for the failure to recognize this condition clinically may lie in the fact that the condition is often not recognized anatomically. It cannot be strongly enough emphasized that often myocarditis cannot be diagnosed on gross examination.

A number of microscopic sections from various regions of the heart must be examined before an exact diagnosis can be arrived at. Such a thorough examination is often not made, and the diagnosis is not made. Thus, for want of such a diagnosis and the inability of the clinician to explain the disease or death correctly on anatomic grounds, the clinician naturally must resort to other spheres for an explanation.

One of the principal purposes of this review is to revive interest in myocarditis with the thought that perhaps more concerted efforts by the

clinician and the pathologist will bridge the gap between the abundance of anatomic changes in the myocardium and their apparent clinical insignificance. That there is sometimes definite clinical evidence of myocarditis in those instances in which the clinician considers such a diagnosis seems clear from the fact that clinically the diagnosis of syphilitic myocarditis is made with relative frequency. Ironically enough, such a diagnosis is rarely, if ever, confirmed by the pathologist.

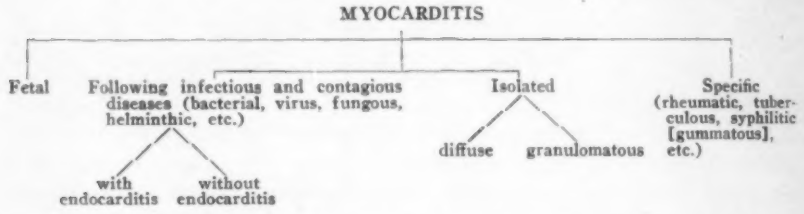
In spite of all this, a search through the literature on myocarditis reveals a number of significant references. The older references are well reviewed by Mönckeberg and by Kirch, and mention of them will be made here only if a full discussion seems warranted. The purpose of this review is to give a clear histologic picture of myocarditis occurring either as a disease entity or as the sequel to a known infectious disease. This will be done by a systematic review of the available references, often extracted verbatim, aided, whenever possible, by a resort to the experience gained in the study of 240 instances of myocarditis, not including the syphilitic group. A pertinent analysis of these 240 instances of myocarditis is given along with the review of the various types of myocarditis, often in summaries interspersed throughout this review as deemed necessary. It is aimed to stress in particular the etiologic moment of the myocarditis from the point of view of diseases in which myocarditis is an important factor, a complication or purely an incident.

Myocardial changes considered the result of primary vascular lesions, such as periarteritis nodosa and endarteritis obliterans, will not be included in this review.

Little is known of the frequency of myocarditis in autopsy material. Neither Mönckeberg nor Kirch stated in their voluminous monographs just how rarely or frequently this condition occurs. Chudějová, reviewing autopsy material in 8,474 cases, mentioned 221 instances of myocarditis. However, included in this series were certain instances of arteriosclerosis, kyphoscoliosis and other conditions. Brown and Hunt found acute myocarditis in 58 of 625 hearts examined microscopically. These hearts were taken at routine autopsies and studied in consecutive order. Albert studied 113 instances of various acute infectious diseases. Myocarditis was found in 46. At the Michael Reese Hospital, Chicago, autopsy material of 5,626 cases was available. In every instance routine sections were cut from the heart but not for the sole purpose of discovering or studying myocardial changes. In this routine material myocarditis was encountered two hundred and forty times. This series of cases did not include instances of contagious diseases or of syphilitic aortitis.

There are many communications on record stressing sudden death in patients with myocarditis. Lisa reviewed the autopsies on 41 patients dying suddenly. In 36 patients there was acute myocarditis. Kolisko, as early as 1913, stressed sudden and unexpected death in myocarditis. He also emphasized that often it is remarkable in the light of the finding of severe and extensive inflammatory changes in the myocardium at autopsy how long the patient lived without impairment of the heart function. More recently, Wuhrmann commented on the sudden deaths of patients with myocarditis. Many of the individual case reports stress sudden death. In particular, mention may be made here of the report by Helwig and Wilhelmy. On the other hand, Hamman, in a study on sudden death stressing ventricular fibrillation as the usual cause of sudden cardiac standstill, hardly mentioned myocarditis. However, he mentioned small areas of scarring or a small infarct as lesions which may inaugurate a fatal rhythm.

A classification of forms of myocarditis is difficult. The old division into parenchymatous or interstitial myocarditis obviously cannot be strictly maintained. Brown and Hunt subdivided myocarditis into acute, syphilitic and tuberculous. Acute myocarditis again was subdivided into nonspecific and rheumatic types. Various classifications of myocarditis have been attempted, but none was found which included all types without overlapping. Purely for didactic purposes the following scheme, by no means either complete or nonoverlapping, is given.



Instead of attempting a classification it seems better to give the following outline of the various types of myocarditis as described in the following paragraphs, arranged according to causes: (1) fetal myocarditis; (2) myocarditis in infectious diseases; (3) isolated myocarditis; (4) myocarditis associated with endocarditis (subacute bacterial and acute bacterial endocarditis); (5) metastatic pyemic abscesses; (6) rheumatic myocarditis; (7) myocarditis associated with infectious granulomas, including those of mycotic origin; (8) myocarditis in virus diseases; (9) myocardial changes in protozoal diseases; (10) myocarditis in helminthic diseases; (11) myocardial changes in thyroid disease, various forms of nephritis, vitamin deficiencies and a few types of chemical poisoning. The last are given fragmentary consideration. For convenience, serous myocarditis is discussed here.

FETAL MYOCARDITIS

While there is an extensive literature on congenital anomalies of the heart in general, reports of myocarditis accompanying these anomalies are rather rare. Reports on fetal myocarditis occurring alone are extremely rare. Myocardial changes accompanying congenital anomalies of the heart are infrequently mentioned in the literature. This possibly is due to the inherent reluctance of the pathologist to take sections from the heart and thus perhaps spoil the specimen. Such changes are apparently more common than one would be led to believe. It is interesting to note in this respect the paucity of illustrations of microscopic sections of myocardial lesions in the atlas of Maude Abbott (1936). The same author in 1926, however, reported myocardial changes in hearts showing defects. She stressed the fact that little has been done to determine the histologic appearances of the myocardium in cardiac anomalies, although there is a rich literature on the inflammatory and degenerative changes that may occur in the myocardium of the infant as a result of congenital cardiac syphilis. In several cases of pulmonary or aortic atresia within her experience the myocardium of the ventricle giving off the occluded vessel showed macroscopically large yellowish gray areas, unmistakably evidencing disease, and revealed microscopically degenerative and inflammatory lesions resembling those described by earlier writers.

Ten years later Abbott stressed that in most cases of pulmonary and aortic atresia there was fetal myocarditis with resulting scarring in the wall of the conus just below the valve. Von Zalka (1924) examined the myocardium in 14 instances of congenital anomalies. In 8 of these the primary lesion was a congenital malformation, and in 6 others the underlying lesion was thought to be fetal endocarditis. It is stressed that the histologic pictures in these two groups were in general similar. There were foci of lymphocytic infiltration, and the capillaries were usually dilated. There was perhaps more proliferation of connective tissue in the second group. It is concluded that the histologic examination of the myocardium may provide a clue to whether the congenital anomaly resulted from a primary malformation or from intrauterine inflammatory changes of the endocardium.

There are cases on record of so-called idiopathic enlargement of the heart. Though some of these may have been instances of von Gierke's disease, in some the enlargement may have been the result of inflammatory changes. It may be of interest to review Stoloff's studies on so-called idiopathic enlargement of the heart in infancy and in childhood. He reported the case of a 15 month old boy who died suddenly. The autopsy disclosed in addition to bronchopneumonia marked enlargement of the heart, which weighed 155 Gm. Microscopic sections showed diffuse infiltration of the myocardium by round cells as well as areas

of degeneration of the muscles. In places the muscle fibers were interrupted by proliferation of connective tissue and only occasionally was there round cell infiltration about a blood vessel. Instances of so-called idiopathic hypertrophy in infancy and childhood were analyzed by Stoloff. Six of the 34 instances reported were excluded from consideration because of some anomaly or abnormality which might have played an etiologic role. In 5 of the remaining 28 instances a histologic examination was not made. It was stressed that a thorough microscopic study is essential to establish the cause and to classify the disease. In 6 of the remaining 23 cases histologic examination revealed myocardial disease, which placed the hypertrophy outside the category of true idiopathic enlargement. There remained then only 17 instances in which the condition of the heart might be considered true idiopathic enlargement. It is conceivable that more extensive histologic examination might have revealed myocardial disease more frequently. The conclusion was reached that when infiltration or degeneration of the myocardium occurs the large heart cannot be considered as showing true idiopathic enlargement. Stoloff insisted that because the histologic picture of the myocardium resembles that seen in many infectious diseases, particularly in diphtheria, it is conceivable that an infection might have caused the condition. However, the definite cause of the myocardial changes has not been established (von Gierke's disease?).

Steiner and Bogin reported an instance of idiopathic cardiac enlargement associated with status thymicolymphaticus in a 3 month old child. The heart weighed 63 Gm. They stressed that microscopically edema with hydropic degeneration of the cardiac muscle fibers was present, but there was no round cell infiltration. The thymus weighed 42 Gm.

Eakin and Abbott in a report of an instance of dextroposition of the aorta and aneurysm of the interventricular septum stated that there was a general increase of connective tissue throughout the myocardium and that in addition there were numerous focal areas of fibrosis replacing the musculature. No inflammatory cells were mentioned.

MYOCARDITIS ASSOCIATED WITH INFECTIOUS DISEASES

In the following paragraphs instances of myocarditis in the presence of infectious diseases and not necessarily associated with endocardial lesions are discussed. Types of myocarditis which are thought to follow focal infections are reviewed. First, myocardial changes encountered in diphtheria and typhoid are discussed in sequence because of their histologic likeness; then myocarditis in paratyphoid and dysentery. Myocardial lesions in measles, mumps and whooping cough are considered next. Myocardial changes following infections of the upper respiratory tract are then considered, particularly that consequent on "influenza" and pneumonia. Because of the distinctiveness of myo-

cardial lesions in scarlet fever, they are reviewed separately. Meager reference is made to myocardial changes in variola and varicella.

Diphtheria.—It is of interest to compare the views of those who believe that diphtheria is capable of inducing true primary myocarditis with the views of those who have not found inflammatory changes but varying degrees of degenerative change in the myocardium. Nuzum described eosinophilic myocarditis in 7 of 29 hearts. This was not present in many instances of death from various other acute infectious diseases. The myocardial eosinophilia bore no relation to the severity of the clinical symptoms or to the degree of myocarditis. A moderate degree of cloudy swelling was found in the bundle of His. He believed that the various types of arrhythmia in diphtheria may be due to compression of the fibers in the bundle of His as a result of moderate cloudy swelling or to the degenerative changes in this system itself. The changes in the conduction system were not proportionate to the degenerative changes present in the myocardium.

Mixsell studied 400 patients, 40 of whom died. Though it is not clear whether or not autopsies were performed, he stated that in 37.5 per cent of those who died myocarditis was the cause of death. He stressed that the most common lesion in the myocardium is fatty degeneration of the cardiac muscle fibers with destruction of the fibers and their transformation into hyalin-like masses. He emphasized two forms of myocarditis, one characterized by an infiltration of plasma cells and lymphocytes in the connective tissue and the other by a proliferation of connective tissue secondary to degenerative changes. In this respect it is of interest to note that de Lange found evidence of healing myocarditis in a 6 year old child whose death resulted from postdiphtheritic polyneuritis.

Kirch stressed the likelihood of parenchymatous degeneration of the cardiac muscle fibers and particularly the necrosis leading secondarily to interstitial myocarditis. However, not every instance of interstitial myocarditis in diphtheria may be explained in this fashion. It seems likely that in rare cases the toxin of Bacillus diphtheriae may act directly as an irritant on the interstitial tissue and thus cause inflammatory changes. The often encountered observation that such inflammation occurs later than the degenerative changes does not necessarily speak against the possibility that the myocarditis occurred independently of the degenerative parenchymatous changes. Kirch was able to grow B. diphtheriae from the myocardium in a large number of cases.

Hoyne and Welford examined 126 cases in which autopsies were made. The heart in each instance was pale, grayish, dilated and flabby. The essential change was found in the myocardium in the form of toxic parenchymatous degeneration. The authors emphasized that in every patient who came to autopsy death was accounted for on the basis of

severe myocarditis. It is interesting to note that the authors emphasized toxic parenchymatous degeneration but subsequently referred to myocarditis.

Dusso reported the sudden death of a 27 year old man. The heart weighed 400 Gm. The myocardium was soft and pink, and the muscle fibers were in part hyalinized. The cytoplasm was granular. Dusso expressed the belief that an attack of diphtheria sixteen years before death had caused this myocardial change.

Oheim examined 50 hearts. The majority of the patients were from 1 to 16 years old, and 1 patient was 32. The earliest change was interstitial edema with spreading of muscle fibers. Myolysis also occurred early. Foci of calcification were observed in 6 hearts between the third and the ninth day of the disease. Fatty degeneration, it was stated, may occur at any time. Cellular proliferations began on the fourth day. Polymorphonuclear leukocytic infiltrations were found on the fifth day and lymphocytic infiltrations on the sixth and seventh days. Perivascular infiltrations were found on the ninth and tenth days. Reparative processes started on the tenth day and were more pronounced on the fourteenth day. The changes were seen more frequently in the subendothelial layer close to the trabeculae carneae and in the region of the base of the heart. The places where the trabeculae carneae and papillary muscles fuse with the heart wall were places of special predilection. Because the right ventricle was often involved, the belief was expressed that the toxin entered the musculature from the ventricular cavity.

Albert examined the hearts of 23 children between the ages of 6 and 11 years. In about 50 per cent of the hearts various degrees of degenerative changes were seen, particularly of fatty degeneration. In the other 50 per cent inflammatory cells were encountered, particularly lymphocytes and more rarely plasma cells and eosinophilic cells. In a few hearts such inflammatory cells were present in the absence of fatty degeneration of the muscle fibers. In spite of this Albert stressed that it cannot be decided whether the inflammatory or the degenerative changes were primary. Two of the hearts which showed only relatively slight changes were taken from children who had died suddenly.

Burkhardt, Eggleston and Smith made an anatomic study of the hearts of 100 patients who died of diphtheria. They stressed that there was a rough parallelism between the degree of change in the conductivity as measured by the electrocardiogram and the severity of the histologic changes in the myocardium. However, there was a distinct lack of correlation between the electrocardiographic changes and the demonstrable lesions in the conduction tracts. As far as gross lesions were concerned, they pointed out that it was a source of considerable surprise to the clinicians to have the pathologist find little or nothing

demonstrable grossly in the heart of a diphtheritic patient who had apparently died of myocardial failure. In the average case the myocardium at most seemed to have lost a little of its tone, and in the more striking cases it was actually flabby. Sections of the musculature might suggest very minor degrees of fatty degeneration with some imitation of "tigroid" mottling. Only in the more severe conditions was frank myocardial degeneration grossly recognizable, and in some cases agonal or antemortem thrombi were seen in the right auricular appendage. Microscopically there were progressive interstitial edema and congestion of the myocardium, which could or could not be demonstrated in the conduction bundles but which usually were especially notable in the auricular musculature, the papillary muscles of the right and left ventricles and the interventricular septum, in that order of frequency. There was also an increasing degree of perivascular leukocytic infiltration into the stroma. In the more severe conditions this extended throughout the musculature but was apt to be patchy and irregular in its distribution. At times it became predominant in the picture. Associated with this interstitial myocarditis were varying degrees of degeneration of the muscle fibers, including fatty and hydropic changes, swelling, loss of staining capacity, ultimately loss of striation and nuclear degeneration (usually of a karyolytic nature) and finally actual necrosis. This paralleled closely the gross changes described. Whether these degenerative changes were the result of direct action of the toxin on the muscle fibers or followed indirectly as a result of the exudation was difficult to ascertain, but arguing by analogy the observers held the former to be the case. A transition of the exudate from the neutrophil to the mononuclear type and a new growth of fibroblasts were observed. This was best demonstrated by special connective tissue stains. These authors also pointed out that the lesions found at autopsy suggested that diphtheria may be one of the causes of chronic fibrous myocarditis in patients who have survived the more toxic state.

From the foregoing description it seems that the investigators concluded that the initial lesions are progressive interstitial edema and hyperemia, which are soon followed by leukocytic infiltration of the interstitial tissue, and that associated with this myocarditis are degenerative changes of varying degrees in the muscle fibers. They did not commit themselves as to the nature of the primary interstitial edema, particularly as to whether or not this lesion may be identical with that to be described in a later section as so-called serous myocarditis.

It is of interest to compare these views with the results of a study of this subject by Warthin in 1924. After reviewing the literature, he presented an analysis of the findings in 16 diphtheritic hearts, stating that the essential lesion was toxic parenchymatous hyaline degeneration or necrosis, associated frequently with fatty degenerative infiltration

and less frequently with cloudy swelling or simple necrosis. The latter lesions were most probably due to accompanying nutritional conditions. Later there was (if the patient survived) a reparative inflammatory process (myocarditis) accompanied by muscle regeneration. Either complete regeneration or fibrosis might result. The toxin of diphtheria might also damage the conducting system. No especial affinity was shown for either apparatus. He further concluded that the conflicting pathologic descriptions given in the literature could be harmonized and the diphtheritic heart given a definite entity of primary toxic parenchymatous degeneration, most frequently of a hyaline nature, followed by reparative inflammation (myocarditis) with muscle regeneration. The histologic picture in any given case would depend on the duration and the stage of the infection, the degree of toxic injury to the muscle, the associated nutritional conditions and the degree of muscle regeneration and accompanying fibrosis.

It thus seems clear that, according to Warthin, the primary changes are degenerative or necrotic in nature and are followed by reparation. Whether or not Warthin was justified in speaking of myocarditis in the sense of reparative inflammation is questionable. Unfortunately, perhaps because of such nomenclature, other investigators have used the term "myocarditis" not to denote simple reparative inflammation but to signify the primary myocardial lesion.

Chiari described a peculiar configuration of the diphtheritic heart, characterized by dilatation of the pulmonary conus, which projects knoblike, as in the beriberi heart. This he explained by the possibility that not all parts of the right ventricle of the heart dilated at the same time but that the conus was involved first.

In this connection it may be mentioned that Gukelberger produced myocardial lesions in 24 of 28 guinea pigs by injecting diphtheria toxins (0.0006 Gm. per hundred grams of body weight). Animals died as follows: 4 three days after the injection; 1 four days, 3 five days, 2 six days, 3 seven days and 3 nine days later. Twelve animals were killed on the eleventh day. In 24 of 28 animals the myocardium showed changes which were diagnosed as diphtheritic myocarditis, though in some instances only simple fatty degeneration was noted. The animals that died early showed principally degeneration and evidence of myolysis. The animals that died later showed varying degrees of true inflammatory changes. Often, transition from degenerative to inflammatory stages were noted. The earliest and the most severe lesions were encountered principally in the middle ring musculature of the heart close to the apex.

In summary, though principally severe degenerative changes are found in the myocardium of the patient with diphtheria, often with necrosis of muscle fibers and edema in the interstitial tissue, later in the disease actual inflammatory changes may be encountered. These changes

are found principally in the interstitial tissue, and often the inflammatory cells assume perivascular distributions. Lymphocytes, polymorphonuclear leukocytes and eosinophilic cells form the inflammatory exudate. These changes may involve the conduction system. The inflammation may heal in the form of diffuse scarrings, giving rise to "fibrosis cordis" *(Kratzeisen)*. Because of Kirch's observation, the question may be raised as to whether or not when diphtheria bacilli are present in the myocardium the resulting changes may not be inflammatory in nature. However, when the damage is the result of the effect of the toxin, degenerative changes may occur. More studies involving cultures of the myocardium are essential to settle this question.

Typhoid.—Chiari believed that true myocarditis in typhoid fever is rare. He stressed the fact that there is principally myocardial degeneration and that inflammatory changes occur secondarily. Mönckeberg, who over a number of years had examined carefully the hearts of patients who had died of typhoid fever, stated that in not a single heart was he able to find changes in the myocardium even remotely resembling those seen in diphtheria. He particularly emphasized that he had never found interstitial myocarditis as depicted by Aschoff. Kirch stated that myocardial changes in typhoid fever are far less common than one would be led to believe from the older literature. LeSage studied the hearts of patients who had died of typhoid fever. Grossly the hearts were flabby, comparable to a wet towel. The myocardium appeared opaque, and the walls were thin. Microscopically there were fatty degeneration and multiplication of the nuclei of muscle fibers. The microscopic diagnosis was acute myocarditis, although the reason for such a diagnosis does not seem clear.

Albert examined the hearts of 6 children and found in 1 fatty degeneration of the muscle fibers just beneath the pericardium and in scattered foci throughout other portions of the myocardium. He stated that "fragmentation" was severe. In another heart a small scar and a few scattered lymphocytes were seen. In a more or less general statement, however, he stressed that fatty degeneration was almost always present and sometimes was accompanied by a slight inflammatory exudate. It was assumed that the fatty degeneration occurred primarily and was followed by an inflammatory exudation in about the third week.

Murray and Kelly, who observed a typhoid epidemic in Calcutta, India, suggested that:

> The myocardial pathology of typhoid fever has been a trifle hastily interpreted by modern thought, which too abruptly dismisses as merely a sign of rapid post-mortem decomposition the toxigenically soft and swollen or flabby heart of the clinical pathologist of former days.

These authors, however, presented no personal autopsy observations.

Porter and Bloom, though they also did not present observations on postmortem material, stated that not 1 of 175 patients who had typhoid fever showed the phenomena characteristic of congestive heart failure. Lately Fishberg emphasized that more recent studies have shown that electrocardiographic changes and evidences of myocardial damage are not rare.

It may be of interest to point out in this connection that Cornil, Poursines and Giraud-Costa constantly found myocardial lesions in guinea pigs infected with the typhoid bacillus. The degenerative changes ranged from loss of the cross striations of the muscle fibers to severe cloudy swelling. Within the connective tissue a nodular or streaky exudate, essentially formed by histiocytes, was present. These lesions were typically perivascular. Edema, hyperemia and small hemorrhages were also encountered. The electrocardiogram showed disturbances of conduction.

Paratyphoid Changes.—As far as myocardial changes in paratyphoid infections are concerned, there is little information in the literature. Though the subject was not mentioned in the text, Mönckeberg showed a photomicrograph of diffuse myocarditis in paratyphoid. Kirch did not mention myocarditis in paratyphoid infections. Kretschmer studied 10 cases in which autopsies were made. One heart showed endocarditis. Among 5 dubious cases there were 3 hearts that showed marked cloudy swelling of the myocardium (paratyphoid organisms were recovered in the duodenum). Two patients had died suddenly, but the hearts showed only hypertrophy.

Wells recorded an instance of acute endocarditis produced by Bacillus paratyphosus B. The heart was enlarged, weighing 510 Gm. A large shelflike vegetation was attached to the middle of the auricular surface of the anterior leaflet of the mitral valve. On the posterior leaflet was a superficial vegetative deposit. The aortic cusps were slightly thickened. Microscopically, the myocardium showed many small foci of acute inflammation with necrosis of muscle fibers and fragmentation of the nuclei of leukocytes. These often were located about fibrinous emboli, but no bacterial masses were found. There were a few small areas of replacement of myocardium by young fibrous tissue. There also was a marked increase in perivascular fibrous tissue not incompatible with healed Aschoff bodies, but no definite rheumatic lesions were present. There was also much fatty infiltration as well as myocardial segmentation.

In this laboratory Meyer and Howell observed an instance of endocarditis caused by B. paratyphosus B and found the heart enlarged, weighing 450 Gm. There was acute vegetative endocarditis of the aortic and mitral valves, superimposed on old endocarditis. Acute mural endocarditis and mycotic aneurysm of the sinus of Valsalva were

observed. The myocardium grossly presented no significant changes; histologically, however, foci of lymphocytic infiltrations, occasional polymorphonuclear leukocytes and endothelial leukocytes were found in some of the perivascular spaces. It seems clear that this was an example of acute paratyphoid B myocarditis.

Dysentery.—In regard to myocarditis occurring in patients with dysentery of any variety Kirch may be quoted, who stated that such a complication may occur occasionally. Knack reported that a 20 year old soldier presented signs of myocarditis a few weeks after having suffered an attack of Hiss Y dysentery. There was no autopsy. Duvernay and Gerbay reported that a patient died suddenly, presumably from myocarditis, after enterococcic infection. Of interest is Sidorov's report on a patient with colitis caused by Balantidium coli who died with symptoms of heart failure. At autopsy the heart was somewhat enlarged and showed a few areas of fibrosis and pale yellow foci located for the most part beneath the subepicardium. Histologically, Balantidium coli was found in the small arteries and also in the myocardium. There were foci of necrosis, at the periphery of which were giant cells of the foreign body type, lymphocytes, a few eosinophilic cells and many fibroblasts.

Measles.—Albert stated that inflammatory changes are occasionally present in the myocardium in measles. However, they are not found before the ninth day of the disease. Insignificant foci of fatty degeneration may be present. One heart contained in the myocardium a recent scar surrounded by lymphocytes and many spindle-shaped cells, and another contained recent granulation tissue. The latter organ belonged to a patient who died on the twenty-first day of the disease. Of 10 hearts which Albert studied, only these 2 revealed myocardial changes; 3 others showed foci of pericarditis, and 5 no changes.

Degen, in an extensive study of 100 fatal cases of measles, stated that pericarditis was present in 4 cases. In 2 there was a shaggy exudate on the visceral pericardium and the pericardial sac was distended with purulent fluid, while in 2 there were lesser amounts of purulent fluid and no fibrinous exudate. Pericardial effusion was somewhat more common, effusion of clear fluid being noted in 23 cases. The heart itself showed no characteristic gross changes. Dilatation of the right side of the heart was found twenty-four times. Of 91 hearts examined microscopically, only 4 showed more than the usual toxic changes. These 4, including the 2 with exudative pericarditis, had cellular infiltration in the myocardium. The infiltration was chiefly lymphocytic and was partially but not predominantly perivascular.

Warthin in 1931 described as the essential lesion of the prodromal stage of measles a subepithelial infiltration of multinucleate syncytial giant cells, lymphocytes and monocytes in the tonsils and pharyngeal

mucosa. Since this discovery there have been several postmortem examinations apparently including examination of the heart, notably those by Semsroth and by Minami. Neither of these investigators mentioned any changes in the myocardium. From the scarcity of pertinent literature it must be concluded not only that true myocarditis is rare in measles but that cardiac complications are rarely encountered clinically. Thus, Schwarzäugel in reporting a recent clinical study of an epidemic of measles did not mention cardiac involvement among the complications observed in this epidemic. It may also be of interest that Kirch in his review did mention measles as a possible cause of myocarditis. Mönckeberg stated that Aschoff and Tawara did not find any changes in the myocardium of a patient who died of measles. He further quoted Loewenthal, who studied 2 instances of measles and 1 instance of measles combined with scarlet fever. In no case was Loewenthal able to demonstrate so-called waxy degeneration in the heart muscle. However, he mentioned that in diphtheria the myocardium showed accumulations of small cellular elements just beneath the epicardium. Such infiltrations were found less commonly in scarlet fever and least commonly in measles.

Mumps; Whooping Cough.—Myocardial changes are rarely found in mumps and whooping cough. Manca reported a singular instance of myocarditis with mumps. The patient was a 21 year old soldier, who contracted the disease during a severe epidemic in the barracks. The myocardium grossly was yellowish pink and opaque and was likened to boiled meat. Histologically, a serous and cellular exudate was seen, consisting of polymorphonuclear leukocytes, some lymphocytes, plasma cells and young fibroblasts. Besides these, there were present large cells with much cytoplasm and round nuclei, whose chromatin formed a coarse "reticulum." There was also cloudy swelling of the muscle fibers. Bacteria were not seen in the sections. In regard to whooping cough Kirch mentioned an instance of a 7 month old child described by Oberndorfer and another described by Vischer. The most extensive studies, however, were made by Brick in 14 cases, in 7 of which microscopic study of the heart was done. In 1 heart (his case 7) a few leukocytes and small accumulations of round cells were found, particularly pronounced within the septum. In another heart (his case 12) occasional leukocytes were encountered throughout the myocardium. In general, eccentric hypertrophy of the right ventricle was the main abnormality of the heart. Fatty changes were also encountered frequently.

Influenza.—Before a discussion of myocardial changes in influenza is attempted, the difficulties of trying to define the exact meaning of the term "influenza" as far as the literature is concerned must be pointed out. There has hardly been any term more loosely used in the past two decades than "influenza" or its synonyms, "grippal infection,"

"flu" or "grippe." It does not fall within the scope of this review to attempt to clarify the exact meaning of the terms used by the various authors, particularly when in the vast majority of reports and studies the exact meaning or definition of "influenzal infection" or "grippe" is not given. It was thought best for this review to use whatever nomenclature was employed by the given investigator. Thus, in the following paragraphs myocardial changes occurring during or following respiratory disease with or without other complications will be discussed, not taking into consideration the agent causing the primary respiratory disease, whether it be Pfeiffer's organism, the hemolytic streptococcus or a virus.

Kirch stated that rarely—as a matter of fact, more rarely than by typhoid fever—true myocarditis is caused by influenza. During the epidemic of "grippe" in Europe in 1918 the hearts of the majority of the patients revealed degenerative changes and, extremely rarely and particularly in the later stages of the disease, inflammatory changes. Schmorl, according to Kirch, was the first to refer to such myocarditis. He described a pure form of interstitial myocarditis with foci of round cell infiltration. The muscle fibers showed scarcely any degenerative changes. The inflammatory changes encountered in the 4 hearts described were interpreted as the result of severe degeneration of the muscle fibers. Three of the patients had died suddenly. Further references are given by Kirch. Lucké, Wight and Kime reported 126 instances of fatal influenza. The majority of the hearts were the seat of recent parenchymatous degeneration and vacuolation.

Wolbach and Frothingham studied the cases of fatal influenza in the epidemic at Camp Devens in 1918 (27 cases). They stated that the heart muscle itself seemed to escape demonstrable injury in this epidemic disease. In 2 instances the endocardium showed an acute lesion on one of the valves, which consisted of a vegetation in which some organization was taking place. The infrequency of this lesion in the endocardium and the fact that in 1 instance a pneumococcus was recovered from the cardiac blood make it unlikely that the cause of the epidemic, whether the influenza bacillus or some unknown virus, was responsible for the changes. In 1 case a small area of cellular infiltration, consisting chiefly of mononuclear cells but with a few polymorphonuclear leukocytes and mast cells, was seen in the tissue about a blood vessel in the myocardium; but this isolated observation was not considered to be of any practical importance.

Miller and Branch reported bacterial endocarditis due to a hemolytic hemophilic bacillus in a 12 year old girl. The musculature of the heart was pale, mottled and nonfriable. The myocardium was studded with infarcts, some almost the size of the low power field; there were also perivascular areas of focal exudative embolic myocarditis, rich in polymorphonuclear leukocytes. These areas were in close relationship

with capillaries and larger vessels, which were filled with cellular and fibrinous thrombi containing polymorphonuclear leukocytes in predominance. However, the infarcted areas, more numerous than the inflammatory lesions, consisted of edematous tissue in which muscle fibers had disappeared and only the framework remained. The periphery of such areas was invaded by newly formed capillaries and fibroblasts, and there was some hemorrhagic extravasation; the contiguous muscle fibers were either vacuolated or appeared homogeneous, without striations or nuclei.

Cabot and Mallory in 1929 presented a case (Cabot case 15161) in which acute endocarditis was probably due to Bacillus influenzae (Pfeiffer). There was associated acute myocarditis. DeSanto and White recorded an instance in which endocarditis was caused by Haemophilus haemolyticus. The myocardium was dark reddish brown, and recent infarcts were noted. Microscopically there were mast cells throughout the interstitial tissue, together with polymorphonuclear and mononuclear leukocytes surrounding coronary vessels. Purulent emboli were seen in the small branches of the coronary arteries. Lichty studied a patient with subacute bacterial endocarditis due to a hemolytic parainfluenza bacillus. The myocardium was uniformly soft, flabby and pale red. Histologically, polymorphonuclear leukocytes and a few round cells were found scattered throughout. There were several areas of necrosis surrounded by fibroblasts. A thrombus (embolus?) with surrounding cellular infiltration was present in one section. The diagnosis was subacute myocarditis with multiple small infarcts.

Fothergill, Sweet and Hubbard reported the case of an 11 year old white boy with subacute bacterial endocarditis, which was apparently due to the saprophytic, avirulent organism known as "Bacillus X." Sections through various portions of the myocardium showed both acute and chronic inflammatory and degenerative changes. In certain areas there were focal accumulations of inflammatory cells between the muscle bundles which were suggestive of the so-called Bracht-Wächter bodies.

Craven, Poston and Orgain recently reported 2 instances of endocarditis caused by Haemophilus parainfluenzae and reviewed the literature on influenzal endocarditis. They also enumerated myocardial changes recorded in the literature. In their first case they found multiple abscesses within the myocardium. In their second the myocardium was firm but extremely pale. Microscopically, the heart muscle was the seat of an acute diffuse inflammatory process, with extensive infiltrations of leukocytes and wandering cells about the blood vessels and in the intermuscular septums, but there was no abscess formation.

Werckmeister-Freund recorded the case of a 21 year old man who had died suddenly. The heart was markedly enlarged, weighing 700 Gm. The enlarged heart was explained as "athlete's heart." Microscopically,

severe degeneration of the muscle fibers with foci of actual necrosis was seen. There was much edema in the interstitial tissue with proliferation of fibroblasts and the presence of lymphocytes and polymorphonuclear leukocytes. These lesions were interpreted as the result of a "grippe" infection which the patient had suffered one and one-half years before he died. This case recalls to mind the myocardial changes described by Schmincke, Hafner and others in instances of "isolated myocarditis" with an influenzal infection as the possible etiologic factor (see later section on isolated myocarditis).

Roulet published 2 instances of myocarditis resulting in sudden death. The hearts were slightly enlarged. Microscopically, the primary changes were thought to be disseminated miliary foci of degeneration and necrosis of muscle fibers. Often only the sarcolemma of muscle fibers remained. Apparently secondarily, there were proliferation of connective tissue cells and infiltration by a few polymorphonuclear leukocytes. Later fine scars were formed. The changes were most marked in the left ventricular wall. In places these changes were similar to those described in so-called serous myocarditis.

Kornblit in a clinical study of 1,212 patients with "grippe" infection stated that 7 per cent showed symptoms of cardiac involvement. There were 80 who revealed what was interpreted as neurocirculatory asthenia, and 5 showed clinical evidence of actual damage. Of these 5, 2 were thought to have endocarditis, 1 myocarditis and the remaining 2 pericarditis. Hamburger stated that influenza, although its exact bacterial or infectious nature is not entirely clear, undoubtedly at times involves the heart. In general, however, involvement of the heart in influenza is infrequent, particularly when influenza is contrasted with rheumatic fever, syphilis or diphtheria.

There are on record a number of other clinical studies on myocardial damage following influenza. Mention should be made particularly of a recent study by Kramàr. On the other hand, Coronini and also Wätjen in discussing influenza and its complications did not mention myocarditis. Brooks stated that evidences of myocardial disease appear frequently in influenza. It may be among the very early indications of influenza or it may appear during the height of the disease, but most commonly it appears in the stage of convalescence. The cardiac lesion commonly caused is myocardial degeneration, occasionally true myocarditis. Sudden death or chronic crippling of the heart is likely to follow this complication.

Thus, from the reports cited it seems clear that myocarditis in so-called grip or influenza is extremely rare, though myocardial damage, which easily may be interpreted as the result of simple cloudy swelling, may be encountered clinically.

The myocardial lesions, both the degenerative and the inflammatory, are apparently similar to, though perhaps more extensive than, those seen in other infectious diseases. At least they are not specific in any respect. In those instances in which Pfeiffer's bacillus has caused endocarditis, changes similar to those encounterd in bacterial or subacute bacterial endocarditis may be found in the myocardium.

The relation of tonsillitis and myocarditis is interesting, and there are many reports in the literature stressing the occurrence of myocardial damage. However, practically all these reports are clinical, perhaps with changes in the electrocardiograms as evidence of myocardial damage. Hamburger and Priest reported structural and functional involvement of the heart following acute infections of the respiratory tract and other infections. However, they did not state the nature of the anatomic damages found. Neidhardt and Thierschmann reported a study of 6 patients with myocardial damage, supposedly the result of "angina." Strauch stressed myocardial damage in infections of the tonsils. Hotz claimed to have found electrocardiographic proof of damage in 60 per cent of his patients with tonsillitis.

Other foci of infection, aside from pneumonia or those which give rise to pyemia, have also been held responsible for myocarditis. Rothschild stated that the role focal infections play in the production of chronic inflammatory lesions in the myocardium is speculative. He had observed extensive focal and diffuse lesions in the myocardium following erysipelas and acute mastoiditis. Wuhrmann attributed to foci of infections the etiologic moment for myocarditis. These foci were: granuloma of a tooth with periodontitis, chronic tonsillitis, bronchiectasis and postoperative bland infections. Among the 240 cases studied there was not a single instance in which an infection of the upper respiratory tract in the sense in which this term is commonly used could have been held responsible for the myocarditis.

It is interesting to compare the views held in current textbooks on this subject. White stated that actual cardiac disease of the nature of bacterial endocarditis is known to follow an acute focal infection, as of a tonsil, a middle ear or the skin. But this happens only in exceptional cases. How frequently slight myocardial damage or a mild endocardial lesion with recovery may occur with such focal infections is not known, but there exists no proof that such a happening is even occasional. Lewis stressed that the term "myocarditis" is scarcely justified clinically except in relation to rheumatism. Perhaps Sprague and White should also be mentioned, who stated that most infectious diseases do little actual damage to the heart and hence terms like "the influenza heart" and "the typhoid heart" are really misnomers. On the other hand, Scherf and Boyd pointed out that commonly local foci, such as those of chronic tonsillar infection, produce myocarditis.

The discrepancies between these views are obvious. Summarizing, then, one notes that little concrete evidence and practically no observations at autopsies are available to answer the question whether myocardial changes occur as a result of tonsillar infections. There are students who believe that fleeting electrocardiographic changes signify anatomic lesions—whatever these may be. There are others, more cautious, who do not accept the statements as to myocarditis in these instances without more anatomic proof than is available today. It certainly is not justifiable to believe that the occasional microscopic myocardial fibrosis or scar in the absence of a demonstrable cause is the result of slight myocarditis which may have followed an infection of the upper respiratory tract. However, it seems that the more severe infections of the upper respiratory tract may occasionally cause myocarditis.

Pneumonia.—Little is found in the more recent literature on myocardial changes occurring in pneumonia. Liebmann's findings (1915) are often quoted. He reported myocarditis in 2 among 11 instances of lobar pneumonia. The myocarditis was characterized by the presence of round cell infiltration about blood vessels within the interstitial tissue. Arnold reported an instance of circumscribed hemorrhagic myocarditis in the region of the sinus node in a 63 year old woman. The patient had pneumonia, and Pneumococcus mucosus was found in the spleen and in the affected portions of the myocardium. Histologically there were polymorphonuclear leukocytes, red blood corpuscles and much edema in and around the sinus node. Stone studied the protocols of 259 autopsies of pneumonic patients. There were 83 instances of lobar pneumonia, 112 of bronchopneumonia and 85 of sepsis following pneumonia. The heart muscle was described as grossly normal in 57.3 per cent of the 89 cases of lobar pneumonia; degenerative changes were believed to be present in 42.7 per cent of the cases. In the 112 autopsies on patients with bronchopneumonia (including the interstitial and confluent lobular types) the gross appearance of the heart muscle was described as normal in 66.1 per cent, and as showing degenerative changes in 33.9 per cent. Microscopic sections of the myocardium were studied in 34 instances of lobar pneumonia and 37 instances of bronchopneumonia. In the lobar pneumonia group 20.6 per cent of the hearts were found normal. Parenchymatous degeneration was found in 52.9 per cent, fatty degeneration in 11.7 per cent, leukocytic and round cell infiltration in 8.9 per cent, hyaline degeneration in 2.9 per cent and interstitial myocarditis in 2.9 per cent. Among 37 hearts from patients who died of bronchopneumonia the heart muscle was normal in 40.5 per cent. Parenchymatous degeneration was present in 37.8 per cent, fatty degeneration in 8.1 per cent, leukocytic and round cell infiltration in 10.8 per cent and interstitial myocarditis in 2.7 per cent.

Swift and Smith reported the case of a 15 year old white girl who entered the hospital with signs and symptoms of generalized peritonitis. Four days later signs of lobar pneumonia appeared. An electrocardiogram two days later revealed a ventricular rate of 47 and an auricular rate of 40 beats per minute with complete dissociation. She died suddenly six days after the onset of pneumonia and four days after the onset of the cardiac irregularity. At necropsy she was found to have marked acute peritonitis, acute pleuritis surrounding the lower lobe of the right lung and a minimal amount of residual pneumonia. The lesions of the lung and pleura were definitely older than those of the peritoneum. A gram-positive diplococcus was identified in the pleural and peritoneal exudates, but cultures were negative. In serial sections of the conduction system there were slight changes in the atrioventricular node, and these changes became more pronounced as the conduction system was followed toward its terminal portions. These changes were characterized by apparent edema and swelling of the cytoplasm of the muscle with granular degeneration. There was loss of striations, and the cells stained paler than normally. The right and left branches of the bundle of His were affected to a marked degree, and in some areas the auricular and ventricular muscle exhibited the same kind of degeneration. The sinoauricular node was normal histologically. Roesler and Soloff described an interesting case, which will also be considered in greater detail. There were unusual anatomic changes in the myocardium. The patient was a 37 year old white man who had had scarlet fever in childhood and influenza fifteen years before death. Three months before death "grippe" developed. Ten days later there was marked shortness of breath with generalized weakness. At the time of admission the blood pressure was 220 systolic and 120 diastolic. During the course of the illness the blood pressure fell and eventually reached 100 systolic and 90 diastolic. The autopsy showed an enlarged heart, weighing 650 Gm. The myocardium was moderately firm and red brown and many long and broad gray streaks were present on the cut surface. The microscopic sections showed in some fields a complete disappearance of muscle bundles, which left a fine reticular or lacelike structure. There was slight infiltration by macrophages, occasional lymphocytes and rarely polymorphonuclear leukocytes. There were also remnants of muscle fibers which had no nuclei or which were hyalinized. The interstitial tissue was increased, and there were many regions of fibrosis and a mild exudate of polymorphonuclear leukocytes, plasma cells, lymphocytes and occasional macrophages. Postmortem blood cultures showed pneumococci type III. The main pathologic diagnosis was hypertrophy of the heart, acute degeneration of the myocardium, fibrosis of the myocardium and subacute myocarditis with focal fibrillar fibrosis of the left ventricle. In addition there were pneumonia and arteriosclerosis of

the kidneys. It was stressed that the peculiar lesion of the left ventricle appeared unique and that it resembled no other type of myocardial lesion with which the authors were familiar.

It must be pointed out that myocarditis is not rarely encountered in instances of pneumococcic endocarditis. Turchetti reported pneumococcic endocarditis. The myocardium showed circumscribed myocarditis with infiltrations of lymphocytes and plasma cells. There was, however, a history of rheumatic polyarthritis. Ruegsegger reported 15 instances of pneumococcic endocarditis with autopsy reports. The pertinent findings in the myocardium were acute focal myocarditis with fibrosis in 1 instance, abscesses in 2 and degenerative changes in 2 others. Lassen, who in 1939 studied 3 patients with pneumococcic endocarditis, found in 1 patient subacute myocarditis. The heart of another had a number of polymorphonuclear leukocytes in the myocardium. Fishkin and Pilot, who studied an instance of pneumococcic endocarditis of the tricuspid valve, stated that the myocardium was soft and flabby but that no focal accumulations of inflammatory cells were noted in the myocardium.

White (1937) stated that pneumonia, either lobar or bronchial in type, may prove a great strain for an already weakened or diseased heart but that it does not itself cause serious heart disease except in rare circumstances, as when acute bacterial (generally pneumococcic) endocarditis or septic pericarditis occurs, either almost always a fatal complication. Among the 240 instances of myocarditis mentioned earlier in this paper, lobar pneumonia was thought to have caused the myocarditis seven times, bronchopneumonia nineteen times and bronchiectasis eight times.

Scarlet Fever.—Albert studied the hearts of 8 patients with scarlet fever, whose ages varied from 1 to 4 years and who were sick for periods varying from seventeen to forty-two days. In 4 hearts infiltrations of lymphocytes and plasma cells were found in the interstitial tissue and also involved the muscle fibers. In 2 hearts simple fatty degeneration was found. These patients died on the twentieth and fortieth days of the illness, respectively. In 2 hearts thrombi were found in branches of the coronary arteries. In 1 heart infiltrations of lymphocytes and eosinophilic leukocytes were found in the endocardium. The belief is expressed that the changes in scarlet fever and diphtheria are somewhat similar. However, the destruction of muscle fibers seen in diphtheria (myolysis) does not occur in scarlet fever.

Stoeber examined the hearts of 22 patients who died of scarlet fever. The ages ranged from 5 months to 28 years. One patient was 50 years old. Six hearts showed no microscopic changes, and in 4 the microscopic changes were minute. The myocardium showed various amounts

of cellular infiltrations. Particularly prominent were faintly stained large oval cells without recognizable cytoplasm, the large nuclei of which showed fine ramification of the chromatin. Transitions to fibrocytes were common. The endothelial cells of blood vessels were swollen. Also present were many histiocytes in addition to plasma cells and leukocytes. It is stressed that the myocarditis of scarlet fever and diphtheritic myocarditis are quite different since diphtheria produces primary degenerative changes in the parenchyma. Hemorrhages in the conduction system may be the cause of sudden death in scarlet fever. Stoeber remarked that the myocarditis of scarlet fever and rheumatic myocarditis may be present in the same patient.

The latter remark is interesting and recalls Schmorl's statement (1914) that he had found typical Aschoff bodies in the heart of a 2 year old child who died of scarlatinal myocarditis. He stressed the fact that there was no history of rheumatic fever. Fahr (1921 *c*), apparently stimulated by Schmorl's report, studied the hearts of 9 patients who died as a result of scarlet fever. The duration of the disease was between three and twenty-eight days. In 4 patients the diagnosis of myocarditis had been made clinically. In not a single instance were rheumatic nodules found in the myocardium. However, minute granulomas were present; they were particularly noticeable around the small blood vessels. These nodules were much smaller than Aschoff bodies, and no giant cells were seen. Four of these 9 hearts also showed endothelial cell proliferations of the endocardium in the form of small nodules. In 3 other hearts only a few such nodules were found, and in 2 they were absent. Kirch, discussing Fahr's papers, concluded that Fahr's studies conclusively showed that the rheumatic nodules (Aschoff bodies) are specific lesions, occurring in no other disease, and must be well separated from the nodules seen in scarlet fever.

More recently Fahr (1930) studied the heart in 11 cases of scarlet fever. He stressed that in 1 instance rather severe myocarditis was present. The most commonly encountered changes were endocardial proliferations in the form of minute nodules. In 2 instances they were marked, in 3 they were less conspicuous, in 4 only a few were present, and in 2 they were absent.

Stegemann stressed the changes in the cardiac ganglions in scarlet fever. These changes varied with the duration and the degree of the disease. The lesions were characterized by round cell infiltrations, fatty degeneration and necrosis of the ganglion cells. Magladery and Billings stressed the difference in the intensity of the myocardial involvement in the various scarlet fever epidemics. Among 37 instances they found 29 with myocarditis, which sometimes was rather slight in extent. But by using the oxidase reaction they clearly demonstrated an increase of

granulocytes. In 1 heart perivascular infiltrations resembling Aschoff bodies were noted. However, this heart also showed acute verrucous endocarditis.

Gardère emphasized that scarlet fever myocarditis is rarely encountered and rarely diagnosed clinically. He also stressed its fatal outcome. The anatomic lesions consisted of interstitial and parenchymatous myocarditis with edema, fragmentation and absence of striation of the muscle fibers. The commonly encountered cells were plasmocytes, polymorphonuclear leukocytes and lymphocytes. This author also mentioned a subacute form of pericarditis.

Dusso reported a case of sudden death in a 19 year old boy. The heart weighed 405 Gm. The left ventricle showed a number of fibrous streaks throughout the myocardium, while the right ventricle was markedly thinned, and in foci muscle fibers were replaced by fibrous connective tissue. There were no lesions of the valves, and the coronary vessels showed no obstruction. No lesions were found in any other organs. The belief was expressed that the changes in the heart might represent old myocarditis, the result of scarlet fever which the patient had had twelve years before death. The author coined the term "sclero-atrophic" for this myocarditis.

Brody and Smith studied the visceral lesions in scarlet fever and related streptococcic infections in a series of 44 cases of scarlet fever and 15 cases of possible scarlet fever in which the heart was examined microscopically. They stated that lesions of varying severity occurred in over 90 per cent of the hearts. These fell more or less into three overlapping types. In all, the chief cell was some form of round cell. The three types were: (1) either a focal or a diffuse interstitial infiltration of the myocardium, having no apparent distribution with reference to the cardiac blood vessels and usually seen in conjunction with either of the following two types; (2) an infiltration either in or about the smaller coronary arteries which took the form of arteritis or periarteritis in which the invading cells were mononuclear, although in some cases there occurred a slight admixture of neutrophilic polymorphonuclears and rarely eosinophils; (3) the commonest type, consisting of a subendothelial infiltration which sometimes occurred beneath the endothelium of coronary veins, more commonly occurred beneath the endocardium of the ventricular chambers but was most striking in the walls of the thebesian vessels.

In summary it seems that myocarditis associated with scarlet fever is rather rare. The inflammation is characterized principally by an involvement of the interstitial tissue, though the cardiac muscle fibers may be replaced by inflammatory cells. The most commonly encountered cells are the lymphocytes, which may be present in the form of

minute nodules, perivascular in distribution. Circumscribed endothelial cell proliferations are relatively commonly encountered in subendocardial regions.

Smallpox; Varicella.—In regard to myocarditis in smallpox, Kirch quoted Aschoff, who apparently had seen inflammatory changes in the myocardium in instances of this disease. Recent references to this subject were not found in the literature. In regard to varicella, H. N. Johnson may be quoted. In a detailed study of a case affecting a 7 month old infant, he could not find any gross or histologic changes in the heart.

NOTE.—For convenience, meningococcic myocarditis, gonococcic myocarditis and tularemia are discussed now before myocardial lesions in subacute bacterial endocarditis and acute endocarditis are reviewed.

Meningococcic Infection.—Judging from the reports in the relevant literature, myocarditis due to meningococci is extremely rare. In a communication on this subject, in 1936, Saphir listed the reported studies and recorded 2 instances. It was stressed that in view of the prevailing opinion that the primary lesion in meningococcic meningitis is meningococcic bacteremia (Herrick), it is not surprising that occasionally meningococci may be the cause of myocarditis. The 2 recorded cases were typical cases of meningococcic myocarditis. Histologically, the condition was characterized by hemorrhagic exudation, early appearance of endothelial leukocytes, destruction of muscle fibers and presence of intracellular gram-negative diplococci. Both patients also showed meningitis with presence of intracellular gram-negative diplococci. In 1 instance meningococci were cultured from the spinal fluid. It is interesting that there was no endocarditis.

Weiss and Wilkins, quoting the autopsy reports of the Boston City Hospital, referred to an abscess of the myocardium caused by meningococci. Hartwell described mitral endocarditis with ulceration in a 13 year old boy. The myocardium showed mottled white, pale brown and red areas. Microscopically, meningococci-like bacteria were present in the vegetations. Within the myocardium were areas of early abscess formation, bacteria surrounded by round cells and smaller numbers of neutrophilic leukocytes. Focal areas of mononuclears and lymphocytes resembling Aschoff's bodies were seen in the interstitial tissue near vessels. The author stressed that there was suppurative myocarditis as well as interstitial myocarditis. A case of possible meningococcic myocarditis was also reported in Lisa's series. M. G. Williams recently reported an instance of meningococcic endocarditis and myocarditis. He stressed that only 20 cases of meningococcic endocarditis verified at autopsy have been reported in the literature. He also emphasized that meningococcic myocarditis, although extremely rare as a single disease

entity, is commonly present in association with meningococcic endocarditis. Williams found rheumatic sclerosis of the mitral and aortic valves, scarring of the myocardium (rheumatic), subacute meningococcic endocarditis and acute myocarditis. There also was meningococcemia but no meningitis. Sections of the myocardium showed swollen muscle bundles, edema and patches of old fibrosis. There was a moderate degree of diffuse neutrophilic and lymphocytic infiltration with perivascular concentrations. Macrophages and eosinophils were also present. Particular attention was paid to rounded pink-staining granular masses within smaller arteries and arterioles, which, however, never completely occluded their lumens. These plugs, which did not take a stain for fibrin, were usually covered by a single layer of swollen endothelial cells. Though no definite conclusion was reached, it was suggested that they may be the result of foci of medial necrosis secondary to the action of bacterial toxins. The myocarditis as judged by microscopic examination certainly was of sufficient severity to have influenced unfavorably the course of the disease. Saphir also stated that it is likely that the associated myocarditis with resulting myocardial failure seriously influences the prognosis, not only because of the myocardial failure but also because the myocarditis is seemingly the result of an overwhelming infection with mennigococci.

As to the incidence of meningococcic myocarditis, the fact that Saphir, paying special attention to the myocardium in instances of meningococcic meningitis, found myocarditis twice among 10 such cases, would indicate that this type of myocarditis is not quite as rare as is generally believed.

Gonococcic Infection.—The same criterion that Karsner postulated for gonococcic endocarditis, namely, the demonstration of the organism either in the circulating blood or in the endocardial lesions, obtains for gonococcic myocarditis. If there has been a demonstration of gonococci within the myocardial lesion, either alone or in conjunction with cultivation of the organism from other sources, there seems no doubt as to the etiologic factor of the myocarditis. The literature on gonococcic myocarditis is scant. There are, however, a number of reports of either single cases or series of such cases of gonococcic endocarditis, in which mention is made of an involvement of the myocardium.

Jagič and Schiffner stated that acute myocarditis and "foci of cellular infiltrations in the myocardium" were the result of emboli. Thayer stated that in gonococcic endocarditis the adjacent myocardium may be involved and suppurating myocarditis result. He also quoted Councilman in this respect. McCants stressed that in gonococcic endocarditis simultaneous myocarditis may be assumed to occur. He described a heart with necrosis of the apical portions and rupture with hemopericardium and sudden death. However, it seems more likely that the

necrosis was the result of infarction brought about by emboli from the vegetations on the aortic valve rather than the result of true myocarditis.

Grenet, Laurent and Levent reported vegetative endocarditis of the mitral and tricuspid valves in a 9 year old girl. There was edema in the myocardium with slight inflammatory changes, more marked immediately beneath the pericardium and endocardium. Diplococci were encountered in the endocardium and myocardium. The blood culture showed gram-negative diplococci.

Kirkland described a subendocardial abscess with extension to the pericardium. Microscopically, the muscle fibers were invaded by leukocytes and organisms. There also was much granulation tissue present. Hoffman and Taggart reported petechial hemorrhages in the myocardium but gave no histologic description.

Solomon, Hurwitz, Woodall and Lamb reported the case of a patient with a positive blood culture and aortic endocarditis. The myocardium grossly was pale red and flabby. Histologically there were edema of the interstitial tissue and infiltration of the stroma by a few lymphocytes and mononuclear leukocytes. Brandes found in a 10 day old infant, whose mother had gonorrheal cervicitis, conjunctivitis of a similar origin and a vegetation on the tricuspid valve. The myocardium showed slight infiltration with polymorphonuclear leukocytes and mononuclear cells, particularly noticeable in scattered areas surrounding the smaller blood vessels. Helpern and Trubek studied a patient who had gonorrheal urethritis and ophthalmia. The autopsy showed ulcerating vegetative endocarditis of the pulmonic valve, from which gonococci were recovered. Beneath the endocardium of the right ventricle the muscle fibers were infiltrated with polymorphonuclear leukocytes. Elsewhere in the myocardium scattered small foci of polymorphonuclear leukocytes were found in the interstitial tissue. Porter reported an instance of endocarditis of the aortic valve. The myocardium histologically showed scattered foci of polymorphonuclear leukocytes throughout the interstitial tissue but no actual abscesses. Degenerative changes in the myocardium were severe. The blood culture was positive for gonococci. Eakin studied a patient with ulcerating endocarditis of the aortic valve. The myocardium showed a few small foci of leukocytes. The blood culture was positive for gonococci.

Staffieri, Ruiz, Sabathié and Minnhaar studied 7 patients with gonococcic sepsis. Included in the study were 3 autopsies. In all 3 there were ulcerating and vegetative endocarditis and an abscess in the interventricular septum. Sabathié stressed the fact that in some instances of gonococcic infection the primary lesion within the heart was found in the interauricular and interventricular septum and only secondarily involved the heart valves. The histologic sections in these instances showed foci of fatty degeneration, extravasations of red blood corpuscles

and, later, phlegmonous infiltration by polymorphonuclear leukocytes, mononuclear and plasma cells. Sometimes abscesses were seen in the myocardium close to the endocardium.

Scolari found large abscesses in the myocardium. There was vegetative endocarditis of the pulmonic and aortic valves. Gonococci were found in the vegetations and in the myocardial abscesses. Nichol and Dobrin studied a patient with gonococcic aortitis, who had a positive blood culture. Within the septum, corresponding to the left ventricle and adjacent to the aortic ring, the leukocytic response was quite intense, and scattered areas of old fibrosis were noted. There also was rather severe cloudy swelling. Their principal diagnosis was acute focal suppurative myocarditis. Rowlands and Simpson reported 8 cases of gonococcic endocarditis, in all of which the blood culture was positive for gonococci. In only 1 instance was a microscopic study of the heart reported. In the sinus of Valsalva was an ulcer which extended into the adjacent myocardium. Abscesses were noted beneath the pericardium and throughout the wall of the right ventricle.

R. H. Williams, studying a series of patients with gonococcic endocarditis, particularly stressed changes in the myocardium in 6 instances. Abscesses and acute focal necrosis were found in 1 heart, acute myocarditis in a second, focal necrosis, septic infarcts, acute focal myocarditis, abscesses and acute focal myocardial necrosis in 4 other hearts. In summarizing his observations Williams emphasized that areas of focal necrosis, sometimes amounting to true miliary abscesses, were present in 6 patients. Lisa mentioned an instance of gonococcic endocarditis and stressed the occurrence of gonococcic myocarditis. Bang recently remarked that the possibility exists that gonococcic myocarditis may be the cause of some chronic cardiac lesions. He also pointed out that in the current textbooks on heart disease gonorrheal infection is never mentioned as a possible cause of myocarditis.

In summary, it seems that isolated involvement of the myocardium in gonococcic infection is rare, though there is an opinion that the myocardial involvement may be prior to the involvement of the endocardium (valvular apparatus). The lesions described are mainly foci of acute myocarditis, foci of necrosis, and inflammations said to occur as the result of direct extension into the myocardium from endocardial or valvular lesions. As may be seen, some of these lesions are quite similar to those encountered in the myocardium in instances of subacute bacterial endocarditis.

Tularemia.—Myocardial changes are also noted in tularemia. As early as 1928 Simpson described fatty degenerative infiltration but not inflammatory changes. Goodpasture and House, however, described a moderate accumulation of large mononuclear cells about the vessels of the heart. Bernstein reported 3 instances. Only in his first case did

he note more nuclei and cells than usual in the interstitial tissue of the myocardium. In the second case microscopic changes in the heart were not mentioned, and as to the third he stated that sections from the heart were normal. Lillie and co-workers, in an exhaustive study on the pathologic character of tularemia with a review of the literature, stated that the heart muscle was studied histologically in 14 instances. In 9 it was substantially normal aside from a variable amount of transverse fragmentation of fibers. Finely granular, cloudy, swollen and poorly cross-striated fibers were seen in 3 instances, and in 1 a diffuse interstitial round cell infiltration was described. Experimentally, they produced tularemia in the Belgian hare. A histologic study of the heart muscle was made in 28 animals with acute tularemia. Focal lesions were seen only in 1 rabbit, which died ten days after the last of three inoculations. The foci were composed of nuclear debris lying among intact muscle fibers. The heart muscle was studied histologically in 61 rabbits with late acute and subacute tularemia. Focal lesions were present in 13. In 4 rabbits there were foci of lymphocytic infiltration and of interstitial caseous necrosis. In 5 others similar necrotic foci were present. Some of these showed a peripheral interstitial proliferation of fusiform fibroblasts or vacuolated epithelioid cells and more or less lymphocytic infiltration. One of these rabbits showed several granulating caseous foci in the atrial aspect of the mitral valve. In the remaining 3 rabbits the focal lesions were granulomatous in general character. Two of these animals showed in the myocardium a few small perivascular nodules of epithelioid cells or fibroblasts with little necrosis and some lymphocytic infiltration. The third showed an area in the ventricular wall, about 1 by 1.5 mm., in which was a dense interstitial proliferation of vacuolated epithelioid cells, associated with compression, atrophy and degeneration of muscle fibers, and a few small (0.1 mm.) foci of caseous necrosis or of polymorphonuclear infiltration. The authors stressed the fact that focal myocardial lesions had not previously been reported in human or animal tularemia.

Foshay reported on an abundance of his own material and also reviewed the literature. He stressed the importance of previous heart disease as causing prolonged disability and mortality. However, he stated that cloudy swelling, loss of striations, fragmentation of muscle fibers and sparsely scattered focal cellular infiltrations between muscle bundles were the only myocardial lesions noted. These lesions were seldom severe or extensive and did not occur frequently. He emphasized further that there is little or no evidence that tularemia seriously damages the normal heart but that a greater probability is that this severely intoxicating infection causes latent coronary disease to become manifest.

The autopsy reports of Stump and Quinn are interesting, though the myocardial changes described apparently have nothing to do with tularemia. The myocardium in 1 patient showed a slight increase of stroma and scattered small numbers of mononuclear cells, denoting still active chronic myocarditis. However, this patient was 56 years old. The second patient had a number of active Aschoff bodies and chronic inflammation in the myocardium. It is likely that the myocardial changes in the first instance were the result of concomitant coronary sclerosis and that those in the second instance were caused by the rheumatic fever which was "incidentally" present.

ISOLATED MYOCARDITIS

Isolated myocarditis is apparently a special though by no means specific form of myocarditis. The pertinent data reported up to 1929 have been given by Scott and Saphir. The condition is portrayed in the literature under various names, such as "Fiedler's myocarditis"; "primarily interstitial, circumscribed, diffuse, isolated myocarditis" and "idiopathic myocarditis." Combinations of terms such as "acute interstitial, isolated myocarditis" are sometimes preferred. The conditions reported as "myocarditis of unknown etiology," "productive myocarditis," "pernicious myocarditis" and "eosinophilic myocarditis" as seen in certain allergic patients apparently belong to this group. In reviewing the pertinent case reports it seems clear that "isolated myocarditis" denotes more or less diffuse inflammatory changes in the myocardium of wide variety and of various causes, having in common principally an isolated involvement of the myocardium by a nonspecific lesion without inflammatory changes of the endocardium or the pericardium. Thus, the rare rheumatic myocarditis (Kramàr) with the presence of Aschoff bodies without accompanying endocarditis or pericarditis does not fall within the scope of the term "isolated myocarditis," nor is pyemia with abscesses in the myocardium (suppurative myocarditis) included. Clinically, isolated myocarditis was characterized by Magner as rapidly progressing myocardial failure often culminating in sudden death. It is noteworthy that in only a few instances was the correct diagnosis made during the life of the patient.

Though Fiedler's own term was "acute interstitial myocarditis," Schmorl (see Šikl), who studied the hearts of Fiedler's patients histologically, definitely described many parenchymatous changes, with actual necrosis of heart muscle fibers and presence of endothelial leukocytes, round cells and muscle giant cells. Also the interstitial tissue was densely infiltrated by mononuclear leukocytes, many of which contained eosinophilic granules.

A review of the literature reveals that two distinct types of myocarditis have been described. One is characterized by the presence of granulomatous lesions and the other by a more diffuse type of inflammation without the formation of granulomas, though so-called muscle giant cells may be present.

Because of such granulomas, which somewhat resemble tubercles or gummas, the possibility of a specific cause is often discussed. Though there is sometimes a history of tuberculosis or of syphilitic infection, neither tubercle bacilli nor spirochetes have ever been demonstrated in the hearts showing this type of myocarditis. Taussig and Oppenheimer reported myocarditis in a 6 year old child with tuberculous mediastinal nodes and sickle cell anemia. These authors stated specifically that there was a proliferative inflammatory reaction with giant cells and caseation as seen in tuberculosis and in syphilis but that no organisms could be demonstrated. The question of syphilis in this instance became particularly pertinent because the child contracted syphilis following a blood transfusion. Granulomas of similar type were also reported by Magner, Šikl (who reviewed the literature), Hansmann and Schenken, Jonas, Sidorov and Miller. Earlier reports were made by Baumgartner, Saltykow and Gierke. This type of myocarditis, sometimes called "granulomatous," though also "isolated" as described, varies from the other reported type of isolated myocarditis in that the lesions are outspoken granulomas, with necrosis. This was pointed out in the discussion of Miller's presentation by Karsner, who stated that the extensive necrosis is not duplicated in isolated acute myocarditis. He also stressed that it is not necessary to exclude syphilis as a cause by virtue of the negative Wassermann test and the inability to demonstrate spirochetes. However, in the same discussion Lillie, diverting attention from syphilis as a cause, pointed out that animals with experimental tularemia not infrequently are found to have granulomatous myocarditis resembling human granulomatous myocarditis (Miller's case).

In contrast to the granulomatous type of isolated myocarditis is the more frequently encountered type which is characterized by diffuse infiltrations of lymphocytes, mononuclear cells, few polymorphonuclear leukocytes, eosinophilic cells and plasma cells. Fibroblasts in small or large numbers are also found. Though principally involving the interstitial tissue, the lesions are present also in the parenchyma with destruction of muscle fibers. Apparently varying stages in the same disease process are described, starting with very cellular stages and culminating in extensive fibrosis. Mural thrombi are commonly seen. Legrand and Nayrac reported an instance of isolated myocarditis with rupture of the heart. More recent reports have been made by Kugler; Legrand and Nayrac; Bessem and Elsbach; Bailey and Andersen; de la

Chapelle and Graef; Boikan; Singer; Maslow and Lederer; Maxwell and Barrett; Simon and Wolpaw; Scott and Simon; Kjærgaard; Freundlich; Lindberg; Smith and Stephens; Helwig and Wilhelmy; Brown and McNamara; Chamberlain.

A series of interesting cases has been reported by Major and Wahl. Each of the 4 patients died suddenly, having had attacks of paroxysmal tachycardia. Microscopically, myocarditis was found. It is possible that these instances also fall into the group of isolated myocarditis.

The occurrence of myogenic giant cells without the formation of granuloma is also occasionally reported in this type of isolated myocarditis. Schultz (1937) may be mentioned, who reported the sudden death of a 21 year old soldier. The myocardium showed diffuse interstitial myocarditis. The muscle fibers were more or less destroyed and were replaced by loose connective tissue and inflammatory cells. A large number of multinucleated cells apparently of myogenic nature were also found. Tuberculosis and syphilis as causative agents were ruled out. It was thought that an inflammation of the tonsils had secondarily caused the changes in the heart.

Though it was mentioned on an earlier page that isolated myocarditis occurs in the absence of endocardial and pericardial lesions, Mittelbach's case is interesting because obviously old slight endocarditis of the aortic, mitral and tricuspid valves was encountered in the heart. There was also recent hemorrhagic pericarditis. The myocardium was firm and had a peculiar shiny appearance, resembling amyloid. The myocardium showed thickening of medium-sized and smaller arteries with absence of nuclei and presence of a homogeneous mass with destruction of the elastic lamellas and occasionally proliferation of the intima. Not rarely giant cells were found in the periphery or close to the masses. The myocardium showed a number of foci of fibrosis and atrophy of heart muscle fibers. Here and there small lymphocytic infiltrations were found with occasional intermingled mast cells. In spite of the fact that the patient had had scarlet fever, measles and typhoid fever, it was not considered that these infectious diseases had produced the myocardial changes. Though the lesions seem more likely to have been rheumatic in origin, the possibility of subacute isolated myocarditis in a heart that happened to be the seat of old rheumatic endocarditis cannot be ruled out.

It is noteworthy that myocarditis of this type also occurs in infancy and childhood. Thus, the series studied by Smith and Stephens included 2 infants, 10 and 13 months old, respectively. Lindberg's patient was 11 months old, Blühdorn's was aged 1½ years, and the patient whose case was reported by Maslow and Lederer was 21 months old. Singer's report on 2 infants who died suddenly may be mentioned in more detail.

The first was a 13 month old infant. In the myocardium a diffuse infiltration of lymphocytes, plasma cells, neutrophilic leukocytes and eosinophilic leukocytes was found. There was also an increase in connective tissue cells. The anatomic diagnosis was subacute diffuse interstitial myocarditis. The second patient was a 6 month old infant who had been well until one day before death. The myocardium histologically showed much vascularized connective tissue replacing the muscle fibers. There were localized infiltrations of lymphocytes, eosinophilic leukocytes and neutrophilic leukocytes and a proliferation of fibroblasts. The author pointed out that the cause of the myocarditis was unknown. He suggested that it might have been a clinically overlooked infection, possibly diphtheria.

Because of the histologic differences of the two types of isolated myocarditis, it seems possible that the etiologic agents are also different. The granulomatous type may very well be caused by a specific organism of unknown variety or one that was not found at the time of the examination. Thus it is possible that either syphilis or tuberculosis may be the underlying cause and that the granulomas signify either miliary gummas or tubercles. It should be pointed out that there are instances on record of granulomatous myocarditis caused by other organisms than the tubercle bacillus or Spirochaeta pallida, such as Blastomyces (Baker and Brian). As mentioned before, Lillie suggested the pasteurella of tularemia as a possible etiologic agent.

In regard to the more diffuse type of isolated myocarditis, the question arises whether or not this is a special anatomic entity or whether a variety of diseases of known or unknown origin may not occasionally involve the myocardium in the absence of recognizable changes in either the endocardium or the pericardium. Various causes have been assigned for this disease, such as burns, infections of the upper respiratory tract, "influenza," toxemias and injuries of the myocardium brought about by such chemicals as sparteine and epinephrine. Recently, Chamberlain reported the case of a patient with a history of alcoholism who at autopsy was found to have isolated myocarditis. As is discussed elsewhere, myocarditis unrelated to endocarditis or to pericarditis occurs during the course of pneumonia and other acute infectious diseases, such as scarlet fever and typhoid fever. As early as 1921 Schmincke reported isolated myocarditis in instances of influenza. Myocarditis is found in hearts of patients with trichinosis in the absence of larvae in the myocardium. Yet these myocardial lesions, though in some instances at variance, often give practically identical histologic pictures. So it seems possible that the scope of the term "isolated myocarditis" must be broadened to include not only those conditions so labeled by the respective authors but also those known to occur

occasionally in a wide variety of infectious diseases. However, there are instances on record of isolated myocarditis in patients who gave no history of infectious diseases that could have caused the inflammatory changes in the myocardium. A number of cases reported as instances of isolated myocarditis would not fall into this group, and segregation of true isolated myocarditis, excluding the granulomatous form, would not be based on histologic criteria but on clinical histories and observations. Magner stressed in this respect the fact that isolated myocarditis constitutes a heterogeneous group including atypical varieties associated with tuberculosis, syphilis, rheumatic fever and disorders of unknown causes. It may be of interest to mention in this connection the study of Gouley, McMillan and Bellet, who described peculiar myocardial changes in pregnancy. However, they did not wish to imply that this form of myocardial change is specifically dependent on pregnancy or on the puerperal state, for they had encountered this condition at least twice in men. The patients usually showed clinical symptoms of cardiac embarrassment. The heart was usually enlarged, weighing about 500 Gm. Histologically, the heart showed focal lesions characterized by disintegration of the myocardial fibers, involving the nuclei to a lesser extent, so that the latter remained as the conspicuous and often major element in the cellular collection that replaced the myocardium. Hemorrhages were rather common, and a moderate number of lymphocytes, macrophages and occasional neutrophils and eosinophils were present. However, the myocardial nuclei were found in practically every active lesion, indicative of a sarcoplasmic degeneration rather than an interstitial infectious inflammation. As the lesions became older, they were invaded by fibroblasts, the original myocardial nuclei disappeared, and ultimately acellular scars replaced the lesions. Occasionally, two or three nuclei were clumped together in small "giant cell" formation at the periphery of the lesion. These authors remarked that the clinical and also the gross morbid anatomic picture in these patients were similar in many ways to those of the rare form of subacute idiopathic myocarditis occasionally reported under the synonym "Fiedler's myocarditis." They emphasized that in a few cases of the latter condition there had been associated parenchymatous involvement with dissolution of the myocardial substance and appearance of "myogenous" cells, similar in some degree to the histologic picture in their material, and it is possible that some of the cases of subacute idiopathic myocarditis were identical with those they observed. However, as far as they could ascertain, no reference has ever been made to pregnancy or the puerperium as having any bearing on the possible genesis or clinical course of the lesion.

Boikan attempted to classify the forms of isolated myocarditis into three groups. The first group embraces the acute forms of isolated myocarditis, the type originally described by Fiedler. Boikan stated that acute myocarditis, though usually causing the death of the patient, might occasionally undergo healing with much new formation of connective tissue. The second group includes the truly chronic forms which invariably cause the death of the patient after disease of several months. Particularly the left ventricle, and occasionally also the left auricle, is involved in these instances. Almost invariably the changes are present in the inner half of the ventricular wall, starting just beneath the endocardium. The initial changes are round cell infiltrations, the cells either localizing in groups or more diffusely infiltrating the interstitial tissues. The capillaries are conspicuously dilated. Later eosinophilic leukocytes are seen, and the muscle fibers become necrotic. Gradually granulation tissue is formed, and eventually foci of fibrosis replace the destroyed muscle fibers. The third group is characterized by the simultaneous presence of recent and old inflammatory changes. Because this is a progressive disease culminating invariably in the death of the patient with the clinical picture of progressive cardiac failure, the term "pernicious" was applied.

Lindberg studied the heart of an 11 month old boy who had died suddenly. There was a history of whooping cough five months before death. Large areas of fibrosis were found, particularly in the wall of the left ventricle, and degenerative changes in the muscle fibers. The most significant change was interstitial edema. Distinct vacuolar degeneration, sarcolysis and myolysis were encountered, combined with atrophy of the muscle fibers. Lindberg compared these changes with those found byWenckebach in the beriberi heart and those described by Rössle and by Eppinger, Kaunitz and Popper as "serous myocarditis." (See later section on serous myocarditis.) It is suggested that in some instances of isolated myocarditis the initial change may be a serous type of myocarditis. The author is impressed with the similarities of the findings in his case with those seen by Boikan.

A few instances are on record in which isolated myocarditis was attributed to unusual etiologic agents, differing from those mentioned. Blühdorn described isolated myocarditis in a child showing an exanthematous lesion of obscure origin and status thymicolymphaticus. Fahr and Kuhle reported 3 instances of myocarditis combined with status thymicolymphaticus in the absence of a previous history of infectious disease. However, Vischer, who studied 5 children with acute primary interstitial myocarditis, observed at autopsy, denied a relationship between myocarditis and status thymicolymphaticus. The patient observed by Maxwell and Barrett had a severe dermatitis due to the use of an ointment containing sulfur. Bernheim-Karrer reported the

case of a 13½ month old infant who died as the result of severe myocarditis. The child had a severe eczema of unknown origin on the cheeks, head and body. Šikl reported that 2 patients dying from severe acute myocarditis had been treated for syphilis with bismuth compounds and neoarsphenamine; one patient possibly had syphilis, the other was in the primary stage of syphilis, and in both a dermatitis developed. Šikl believed that the myocarditis may have been of an allergic nature occurring perhaps on the basis of a special idiosyncrasy to either bismuth or neoarsphenamine. Stöckenius reported 4 patients with syphilis in whom a dermatitis developed in the course of arsphenamine treatment. Two of these patients revealed myocarditis at autopsy. As in Šikl's cases, there were granulomatous lesions in the myocardium. Though Stöckenius expressed the opinion that these lesions were the result of rapidly spreading syphilis in spite of the absence of spirochetes, Šikl, after restudy of the pertinent sections, concluded that the myocardial changes, just as the lesions of the skin, could be better explained as the result of a peculiar hypersensitivity to arsphenamine. Ucke studied a young woman, 18 years old, who died rather suddenly after an attack of severe pain in the upper part of the abdomen. Histologically, the myocardium showed marked infiltration of the interstitial tissue by inflammatory cells. Many of these were plasma cells. The striations of the muscle fibers could not be made out, and actual myolysis was observed. The belief was expressed that this myocarditis was of toxic origin, on the basis of an allergy or a hyperergic condition.

Nelson reported an instance of exfoliative dermatitis in a patient who, because of a strongly positive Wassermann test, was treated for syphilis with a bismuth compound and neoarsphenamine. Severe cardiac symptoms developed, and diffuse myocarditis was found at autopsy. The cause of the dermatitis was thought to have been the cause of the myocardial lesions. Another somewhat similar instance of dermatitis following arsphenamine therapy was reported by von Zalka. Instances of diffuse myocarditis in patients with exfoliative dermatitis were also reported by Brown and McNamara. As will be shown elsewhere, a number of investigators expressed the belief that rheumatic myocarditis constitutes an allergic phenomenon. It may be pointed out that the changes described both in the hearts of patients with rheumatic fever and in experimental animals do not at all resemble those seen in isolated myocarditis.

Franz discussed a patient who for a number of years had been treated with epinephrine because of bronchial asthma. At autopsy the myocardium showed foci of fibrosis with a few lymphocytes and fibroblasts. In some fields the connective tissue spread in the form of a network, leaving some of the muscle fibers preserved within the holes

of the net. However, Franz stressed that the fibers of the heart muscle were apparently primarily damaged, perhaps as a result of the administration of epinephrine or possibly because of a definite hypersensitivity toward this substance.

It should be mentioned in this connection that Hansmann and Schenken in their report on acute isolated myocarditis remarked that in the experimental production of acute myocarditis the best results were obtained by the method, among others, of combining sparteine with epinephrine. They stated, however, that the lesions produced are not comparable in severity with those of acute isolated myocarditis.

These observations are extremely interesting because they suggest a common etiologic factor, a possible peculiar hypersensitivity (allergy) to chemicals or perhaps, though not likely, syphilis. Brown and McNamara, who reported a case of acute interstitial myocarditis following administration of arsphenamine, may be quoted:

> In the light of our present knowledge, therefore, the acceptance of the allergy hypothesis to explain the myocardial lesions of arsphenamine dermatitis rests on the exclusion of other causes on morphologic grounds and on the compatibility of the lesions with those encountered in other types of known allergy.

It must be noted, however, that in some of the aforementioned instances the myocarditis was diffuse, and that in others it was granulomatous, in type.

A number of patients with isolated myocarditis died suddenly. Magner's patient, who died suddenly after thyroidectomy, may be especially mentioned. Helwig and Wilhelmy, who reported the cases of 3 patients dying suddenly, stressed that interstitial (isolated) myocarditis constitutes a definite, important and perhaps not infrequently unrecognized cause of sudden death.

In summary it may be stated that isolated myocarditis often causes rapidly progressive myocardial failure or sudden death. Isolated myocarditis may be divided into two types, one characterized by the presence of granulomatous lesions, and the second by a more or less diffuse inflammatory lesion, of the myocardium. The granulomatous form presents a clearly outlined anatomic picture, resembling other known types of granulomas. Various etiologic agents have been held responsible for these granulomatous lesions. Often syphilis or tuberculosis is suspected. Lately, a special form of hypersensitivity, particulary that to arsphenamine, has also been held responsible for this type of myocarditis. As long as the origin of this form is not known the term "granulomatous" seems adequate. Whether or not the diffuse inflammatory type of myocarditis should be set aside and marked specifically is questionable, since histologically similar types of myocarditis occur in various infectious diseases. Perhaps as Gouley, McMillan and Bellet stated, the term "Fiedler's myocarditis" or "isolated myocarditis" as used for the second

variety is little more than a convenient name for myocardial inflammations that do not fall into standard classifications. Yet, from a review of the literature presented, it is clear that one is justified in accepting the occurrence of isolated myocarditis in the sense of a more or less diffuse inflammatory lesion if every known cause for this type of myocarditis is ruled out and if the myocarditis is found in the absence of any major pathologic condition involving either the endocardium and pericardium or the entire body. That such myocarditis occurs seems clear from the study of the aforementioned 240 instances of myocarditis, among which were 15 cases of isolated myocarditis of the type just mentioned.

MYOCARDITIS ASSOCIATED WITH ENDOCARDITIS

Subacute Bacterial Endocarditis (Endocarditis Lenta).—Saphir in 1935 reviewed the literature pertaining to myocardial involvement in subacute bacterial endocarditis and reported myocardial changes encountered in 35 hearts with subacute bacterial endocarditis. Among earlier observers, Blumer stated that the myocardium was relatively slightly involved in subacute bacterial endocarditis. Libman in 1923 and 1926 found round cell interstitial infiltration which, however, was not present in all instances and was not specific. He considered myocardial insufficiency as a determining factor in the causation of death. Thayer (1926) stated that the myocardial lesions were generally subsidiary. Rothschild, Sacks and Libman stressed that in the majority of cases focal lesions consisting of cellular infiltrations were found. Clawson (1928 *a*) reported greater frequency of abscesses in subacute bacterial endocarditis than in other forms of endocarditis. Hamman and Rich (1933), in a study of 2 cases, found the myocardium normal in the first and observed focal areas which represented scarring of the myocardium in the second. There were also minute infarcts and an occlusion of a small branch of the coronary artery by an organized thrombus. Fragments of infected vegetations were encountered in branches of the coronary arteries.

Perry stated that the only pathologic changes in the myocardium were cellular foci, which were first described by Bracht and Wächter. In 9 consecutive cases such cellular foci were found in all but 1.

Cornil, Mosinger and Jouve reported that at autopsy in cases of subacute bacterial endocarditis myocarditis is found more frequently than has been generally accepted. The most commonly encountered changes are degenerative interstitial myocarditis, which is particularly pronounced in the subendocardial regions and consists of histiocytic infiltrations, mostly perivascular in distribution, and scars. They also reported the presence of infarcts. De Navasquez studied the incidence and genesis of myocardial lesions in 20 hearts with subacute bacterial endocarditis. He found myocardial lesions in 19 of these hearts. The

lesions consisted of bacterial emboli and foci of polymorphonuclear leukocytic infiltrations. In regard to Bracht-Wächter bodies he indicated that the term should not be used because of its ambiguity.

Buchbinder and Saphir stressed the occurrence of heart failure, clinically and anatomically. They observed extensive myocardial lesions uniformly. These consisted of emboli, minute infarcts, abscesses, diffuse inflammation, Aschoff bodies and perivascular fibrosis.

In a study previously mentioned Saphir (1935) noted changes in the myocardium as follows: Petechial hemorrhages were found occasionally, apparently having the same cause as those found in other locations in subacute bacterial endocarditis. Typical abscesses were often present in addition to foci of necrosis. These abscesses were apparently the result of lodgment of small bacterial emboli in minute vessels or capillaries. Acute inflammatory changes without the formation of abscesses were sometimes encountered, which were particularly pronounced in the interstitial tissue and consisted mostly of infiltrations of polymorphonuclear leukocytes and a few lymphocytes. (Clawson stressed that abscesses are found in greater frequency in subacute bacterial endocarditis than in other forms of endocarditis.) Foci of perivascular infiltrations of lymphocytes were quite distinct. These lesions did not resemble Aschoff bodies. They were circumscribed subacute or chronic inflammatory lesions confined to the perivascular spaces. Organizing infarcts were the most commonly encountered lesions. They consisted of many spindle-shaped cells arranged in parallel rows replacing the heart muscle fibers. Occasionally lymphocytes were seen scattered among these cells. Phagocytic cells were often noted, their cytoplasm filled with a reddish brown granular pigment. There was also a scant new formation of connective tissue fibers, and often several small-sized blood vessels extended through these regions. Frequently emboli were noted, consisting of thrombi (mainly fibrin and polymorphonuclear leukocytes or rarely of what obviously was a portion of a broken-off vegetation). Though occasionally recent and older infarcts were seen, the organizing infarct was the lesion most commonly encountered in the myocardium.

Aschoff bodies were also noted. In Clawson's series of 60 cases of subacute bacterial endocarditis Aschoff bodies were found in 27. In the material at the Michael Reese Hospital, Chicago, typical Aschoff bodies were encountered in 14 of 35 hearts. Thayer found Aschoff bodies associated with abscesses in the myocardium in 1 heart. Perivascular areas of fibrosis which are quite often seen in instances of subacute bacterial endocarditis may possibly be taken as the healing stage of Aschoff bodies. In our material comprising 35 hearts with subacute bacterial endocarditis, the most commonly encountered lesions were

those described as small or minute organizing infarcts. These were also considered as the most characteristic myocardial change.

In a number of reports the presence of Bracht-Wächter bodies is stressed. It may be of interest in this connection to point out the nature of these bodies and their significance. Bracht and Wächter described minute and larger areas of necrosis surrounded by lymphocytes and fibroblasts in the myocardium of a rabbit given five injections of 2 or 3 cc. of broth cultures of Diplostreptococcus rheumaticus at forty-eight hour intervals. The myocardium of rabbit 2, which received four injections over a period of fourteen days, revealed irregularly distributed, more or less well defined cellular infiltrations situated mainly in the interstitial tissue. Occasionally these foci extended into the muscle fibers themselves. A few necrotic muscle fibers with calcification were seen. Most of the cells were lymphocytes. Fibroblasts and occasionally plasma cells were also present. The myocardium of rabbit 3, which received four injections over a period of sixteen days, revealed long, spindle-shaped, threadlike connective tissue nuclei and streaks of fibrosis in the midst of the muscle fibers.

From this description it is difficult to determine just what a Bracht-Wächter body is. This is particularly so because of the location of the lesions described by these authors. The lesions of rabbit 2 were found principally in the interstitial tissue, while the lesions of rabbits 1 and 3 were found predominantly within the parenchyma. If the lesions found in rabbit 2 are regarded as Bracht-Wächter bodies, it must be considered that their description suggests the perivascular infiltrations seen in the myocardium in cases of subacute bacterial endocarditis. It is interesting to note, however, that Rothschild, Sacks and Libman described Bracht-Wächter bodies as follows:

> Examination of the myocardium in subacute bacterial endocarditis discloses in the majority of cases focal lesions consisting of cellular infiltrations (chiefly of round cells) in areas where the muscle fibers have undergone degeneration or necrosis. These are the so-called Bracht-Wächter lesions which differ from the Aschoff bodies in certain essential particulars. They are frequently inconspicuous in size and distribution, but at times they are widely diffused throughout the myocardium, and the individual lesions may assume considerable proportions.

Libman (1923-1924) stated:

> In cases of subacute bacterial endocarditis there is often a focalized lesion in the myocardium known as the Bracht and Wächter lesions. These are foci which consist mainly of lymphocytes and are found in the muscle fibers themselves—the Aschoff bodies being found outside the muscle fibers. The Bracht-Wächter bodies have been reproduced experimentally, but nobody has been able to reproduce the Aschoff bodies.

Bishop, Bishop and Trubek mentioned Bracht-Wächter bodies as observed in cases of subacute bacterial endocarditis. They described them as scattered cellular accumulations consisting of large mononuclears, neutrophils and lymphocytes. This description, especially as far as location is concerned, corresponds much more to that of the lesions produced by Bracht and Wächter in rabbit 3.

Rothschild in illustrating early embolic myocarditis showed a typical abscess with the bacterial embolus in the center. This lesion he called a Bracht-Wächter body.

Perry, in a report previously mentioned, stated that Bracht-Wächter bodies are almost certainly embolic in nature and are closely paralleled by similar findings in other organs. In the photograph the Bracht-Wächter bodies appear as accumulations of polymorphonuclear leukocytes with masses of bacteria in the center (seemingly abscesses).

Because of the uncertainty of just what constitutes a Bracht-Wächter body, and because from the original description apparently three types of lesions have been designated as Bracht-Wächter bodies, it seems wise to discard the term "Bracht-Wächter bodies" entirely and to use rather descriptive terms for lesions which by some investigators might be called Bracht-Wächter bodies.

In 44 of the 240 instances of myocarditis previously mentioned this condition occurred with subacute bacterial endocarditis. (See sections on myocardial lesions in gonococcic myocarditis and pneumonia and pneumococcic endocarditis.)

Whereas myocardial lesions occurring remote from the endocardial lesions in cases of subacute bacterial endocarditis are reported rather infrequently, inflammatory lesions of the endocardium extending directly into the myocardium are not rare. Only Kidd's case may be mentioned here. It was an unusual instance of sudden death following mycotic ulceration of the conduction system. The mycotic ulceration had almost perforated the ventricular septum.

Acute Bacterial Endocarditis.—Inflammatory changes in the myocardium are commonly encountered in instances of acute bacterial endocarditis. In practically every instance of this type of endocarditis the myocardium on careful examination will show foci of acute inflammation, particularly pronounced in the interstitial tissue. As early as 1923 Libman pointed out that whenever lesions are found in the heart muscle in acute bacterial endocarditis they consist in the main of polymorphonuclear leukocytic infiltrations. Rosenthal, describing branch arborization and complete heart block, discussed 2 cases in which the myocardium showed inflammatory changes. In 1 heart portions of the membranous and muscular septums were the seat of extensive extravasations of blood, about which were many polymorphonuclear leukocytes.

There also were polymorphonuclear leukocytes and round cells in a perivascular distribution. It is interesting to note that whereas the aortic valve was normal grossly, histologically it showed necrosis with presence of polymorphonuclear leukocytes. The microscopic diagnosis was ulcerative suppurative endocarditis of the aortic valve and suppurative hemorrhagic interstitial myocarditis. The cause of the myocarditis was not stated but the author remarked that microscopic lesions of the valves should not be overlooked in the genesis of myocarditis in that it is often hard to decide whether the lesions of the valves preceded or were concomitant with the myocarditis. This case is interesting and bears out the importance of careful examination of the cardiac valves in determining the origin of myocarditis.

Among the 240 instances of myocarditis there were 14 in which this condition was present with acute bacterial endocarditis.

ABSCESSES IN THE MYOCARDIUM

Though reports of abscesses in the myocardium are unusual, there seems to be no question that such abscesses occur quite often. As a matter of fact, in every instance of pyemia abscesses may be expected in the myocardium. Among the 240 instances of myocarditis which I have observed, abscesses in the myocardium were encountered in 32. In these cases, pyemia was present, and the abscesses were not related to any form of endocarditis. The older literature was reviewed in great detail by Mönckeberg. Lawrence and Scott reported observations on a patient who had a myocardial abscess and who died suddenly following a surgical operation. Weiss and Wilkins, (1937 *c*) stated that abscesses of the myocardium are relatively rare and that literature on this subject is meager. They stated that in most instances such abscesses are a metastatic manifestation of an overwhelming sepsis and of more theoretic than clinical significance. They quoted the necropsy reports of the department of pathology at the Boston City Hospital. Abscesses in the myocardium were noted in 31 cases, with bacteriologic data available in 26. Staphylococcus aureus was responsible for the sepsis in 20 cases, pneumococci in 2, Streptococcus viridans in 2, Streptococcus pyogenes in 1 and meningococci in 1. These authors give details of the history of a 73 year old white man who at autopsy showed a pericardial cavity filled with blood. There was a rupture of the right ventricle below the base of the pulmonic valve. Over this area the myocardium was pale gray-brown and showed a few small irregular yellowish points. Histologically, surrounding the ruptured area was a marked diffuse neutrophilic infiltration of the pericardium and myocardium with acute necrosis of the heart muscle. Gram-Weigert stain showed numerous gram-positive cocci in pairs and clusters in the abscess area. Bacteriologic

examination of the blood obtained from the cardiac cavity yielded a pure culture of Staph. aureus. These authors referred to reports of 7 instances of rupture of the heart by abscess in the literature in which the descriptions were sufficiently detailed to rule out other conditions.

Among the cases of spontaneous cardiac rupture collected and analyzed by Krumbhaar and Crowell, abscesses were mentioned in only 3 and myocarditis in 4. Of 92 additional cases of ruptured heart analyzed by Davenport, the rupture was the result of an abscess in 2.

As was shown in the foregoing sections, abscesses in the myocardium are also encountered in acute and subacute bacterial endocarditis.

RHEUMATIC MYOCARDITIS

During the past two decades or so, much attention has been focused on rheumatic fever, rheumatic endocarditis and the accompanying myocardial lesions. In this general review it may suffice to state that principally there have been two apparent causes for the recent revival of discussion. One was the finding of streptococci (nonhemolytic—Zinsser and Yu) in the blood and also in the myocardium and spleen of patients with rheumatic fever. After these studies became known, the question was once again raised as to the possibility of streptococci being the cause of rheumatic fever. The second cause, closely linked with the supposed streptococcic origin of rheumatic fever, was the hypothesis that rheumatic endocarditis and subacute bacterial endocarditis were manifestations of the same disease, differing only in the immunologic response of the patient. It seems clear that, though allergy forms an attractive explanation for these two diseases, this explanation is at best a hypothesis founded on animal experiments and speculations which still remain to be proved. Swift stated that the experimental demonstration of hypersensitive and immune reactions to streptococci seems transferable by analogy to the clinical conditions of patients with rheumatic fever and with subacute streptococcic endocarditis, respectively. He was not able, however, to produce in experimental animals the pathologic picture which is considered characteristic of rheumatic fever. The difference in the diseases is supposed to lie in the difference in the reaction of the host.

Though it is established that allergy plays an important role in many diseases, it is generally clear that some of these diseases are caused by specific agents. If it is considered that rheumatic fever is solely an allergic phenomenon, it must be assumed that the tissue reactions in rheumatic fever are similar to those seen in experimentally produced allergic inflammations. Thus, the Aschoff body in the myocardium would be considered as signifying a nonspecific inflammation. In other words, since rheumatic fever has been considered an allergic phenomenon, the significance of the Aschoff body has again aroused much

discussion. The question is invariably asked whether rheumatic myocarditis, characterized by the presence of Aschoff bodies, should be regarded as a specific disease entity of unknown cause or as a hyperergic reaction brought about by certain types of streptococci. It seems clear that the supporters of the allergy theory must discard the Aschoff body as the specific histologic entity of rheumatic myocarditis. Otherwise they cannot assume that the Aschoff body signifies merely a hyperergic reaction of the patient to a nonspecific cause. Also the simultaneous presence of Aschoff bodies and abscesses in the myocardium, as shown by Saphir (1935) and more recently by Lisa, speaks offhand against the assumption that rheumatic fever is an allergic response and that the Aschoff body can be considered an example of a hyperergic reaction.

It is interesting to note that while Aschoff described the characteristic nodule which was held to be specific for rheumatic fever in the myocardium in acute rheumatic endocarditis, Schmorl mentioned the observation of such nodules in 1 instance of scarlet fever. Fahr (1930) in an extensive study showed that nodules seen in the myocardium of patients who died from scarlet fever indeed resembled somewhat those seen in rheumatic fever but were not at all identical. But it seems that since Schmorl's report there has been confusion in the literature, and many investigators have claimed that they produced Aschoff nodules experimentally. However, close scrutiny reveals that these nodules do not at all conform to Aschoff's original description. It is interesting in this respect to review the proceedings [1] of the American Association of Pathologists and Bacteriologists in 1929 and 1930 in regard to the discrepancies of opinion as to the criteria to be used in identifying Aschoff bodies.

Most students in this field distinguished three stages in the development of rheumatic lesions in the myocardium. The first stage is characterized by edema of the connective tissue (serous inflammation) and by intense eosin staining of the ground substance in the collagenous bundles. Later, the individual fibers cannot be distinguished and a homogeneous waxy appearance of the conglomerated fibers results. The thus altered tissue assumes the staining characteristics of fibrin, and this similarity is responsible for the name, "fibrinoid swelling" (Klinge, 1930). Gross and Ehrlich (1930) and Klinge (1930) observed that the connective tissue fibrils are intact, though dissociated, and that with silver impregnation it is possible to stain the fibers black, whereas the unchanged fibers stain brown. The fibrocytes appear shrunken, as if dehydrated. There is also a moderate infiltration of round cells, which have round nuclei and scanty cytoplasm and are indistinguishable

1. Am. J. Path. **5**:531, 1929; **6**:621, 1930.

from lymphocytes. Their origin, according to Gross and Ehrlich, is uncertain, and it cannot be decided whether they are true lymphocytes or elements of fibroblastic or histiocytic derivation; for that reason Gross and Ehrlich suggested the name "mesenchymal cells." It seems that these cells are the chief constituents of the so-called "monocytic-lymphocytic nodules," to which attention has been drawn repeatedly during recent years in the interpretation of the lesions resulting from attempts at experimental reproduction of rheumatic fever. Besides these elements, a few neutrophilic or eosinophilic leukocytes are also frequently observed in this lesion.

The first stage was described by Talalajeff, under the name of "disorganization stage." It was apparently rediscovered by Klinge (1930), who called it "early rheumatic infiltration."

In some instances these fibrinoid lesions may be absent, but in other cases they may be so intense as to simulate a severe degenerative-necrotic process indistinguishable from that seen sometimes in instances of acute nonspecific septic processes (Klinge).

In the second stage there are proliferation and hypertrophy of the connective tissue cells, which eventually fuse to form giant cells. The giant cells finally may predominate, and the typical granuloma is formed (Aschoff nodule).

The Aschoff nodules are very small submiliary bodies, located around vessels and often but not always in relation to the adventitia of medium-sized or small vessels. The nodule is formed by accumulation of large cellular elements with one or more large nuclei, the contour of which is lobate or polymorphous. The general distribution of the nuclear elements resembles a fan. In the center of the body necrotic foci may be found.

The giant cells of the Aschoff body are of considerable size, but much smaller than those seen in tuberculosis or in the foreign body granuloma. Their cytoplasm is more or less abundant and slightly basophilic. Their most important characteristic is the appearance of the nucleus, which is relatively large, lobular or "budding." Often more than one nucleus is found in a cell. However, the number of nuclei is always very small; they are in close approximation to each other, exhibit marked polymorphism and are located centrally.

In addition to these elements there are variable numbers of endothelial leukocytes (epithelioid cells), lymphocytes and polymorphonuclear leukocytes, especially eosinophils.

A more detailed study of the Aschoff nodules may show many varieties, which are differentiated according to the disposition and the number of their constituent elements. Gross and Ehrlich (1934) in a very careful study were able to separate seven different types.

Eventually the Aschoff granuloma is slowly transformed into a scar (the so-called third stage). According to more recent investigators, it is also possible, though not yet proved, that scars may directly follow the exudative lesions of the first stage, without having reached the granulomatous stage. In fact, Rössle (1935) and Morpurgo maintained that even the very early serous inflammation may heal with the formation of a scar.

Geipel, Takayasu, Talalajeff, Gross and Ehrlich (1934) have been interested in the question of just when the anatomic lesions appear in the myocardium during rheumatic fever and how long they persist. It seems important to establish whether or not it might be possible to draw conclusions as to the duration of the disease from the anatomic picture of the lesion. Their studies seem to indicate that the first stage of the rheumatic granuloma may be found from the second to the fourth week of the disease. The second stage is said to be developed about the fifth week and the scar is established between the third and the sixth month.

According to Andrei and Ravenna, this time must be considered as the shortest time required for the formation and the evolution of one lesion. They stressed that nobody knows just how long a granuloma persists, even a granuloma produced experimentally by a known agent. They also emphasized that it is now generally admitted that a tubercle may be present for years and that the disease process becomes activated when local or general conditions of the host permit. For the same reason they expressed the belief that the presence of an Aschoff nodule is neither definite proof of active rheumatic carditis nor evidence that a phase of activity has occurred recently. Clawson (1940) may be mentioned here, who found Aschoff nodules in 13.84 per cent of patients who had completely healed lesions of the heart valves and in 10.44 per cent of those who had calcifications of the aortic valve (including arteriosclerotic calcification).

The presence and the frequency of the Aschoff body as occurring in its first stage are still subjects of discussion. Aschoff (1934) himself, though admitting the possibility of their presence for theoretic reasons, stated that in his own investigations he never was able to discover exudative lesions of the type of the "fibrinoid swelling" unaccompanied by cellular reaction.

The mechanism of the fibrinoid lesion itself is also a matter of discussion. Though Klinge and others described it as a typical and true degenerative process of the connective tissue, others expressed the belief that the fibrin-like appearance and reaction of the tissues were due merely to exudation of plasma and infiltration of the connective tissue with true fibrin. This opinion was held particularly by Clark, Graef and Chasis and by Graef, Berger, Bunim and de la Chapelle.

So much for more recent descriptions of the rheumatic lesions in the myocardium. As can be seen, the only characteristic lesion in the myocardium in rheumatic fever is the so-called second stage, namely, the Aschoff body. While there are distinct variations, without any question correlated with the age of the Aschoff body, it must be stated that morphologically the diagnosis can be made only if a clearcut Aschoff body is recognizable in the heart. In this respect Saphir and Wile may be quoted, who emphasized that the characteristic Aschoff bodies invariably consisted of infiltrations of large cells often showing a basophilic cytoplasm containing one, two or three nuclei, a few lymphocytes, and an occasional plasma cell and polymorphonuclear leukocyte. These accumulations of cells were almost always found in the vicinity of the blood vessels. Occasionally, necrotic foci or a fibrin-like material was encountered in these areas. The large cells were seen in parallel rows, often assuming a typical palisade arrangement. The internal structure of the nuclei of some of these cells could be compared with that of a spider web. Apparently depending on the pressure of the surrounding tissues, the cells were either compactly arranged, the Aschoff bodies presenting an elongated appearance, or were well separated from one another, the Aschoff bodies appearing rather square or round. A discussion of the origin of the large cells would far exceed the scope of this communication; it may merely be stated that these cells are believed to be polyblasts rather than myocytes. The various routine stains for bacteria failed to reveal micro-organisms within the Aschoff bodies.

Perhaps it might be mentioned here that recently Wilson in an extensive study on rheumatic fever concluded that the earlier concept of streptococcemia as a cause of rheumatic fever is no longer tenable and that the present incomplete knowledge of the fundamental factors underlying the concept of allergy in human disease permits only speculation as to the possible role of allergy in rheumatic fever.

The aim of the morphologist is to recognize the nature of the disease, relying as much as possible on the gross or the histologic features alone. It is clear that this cannot always be done, perhaps because of present limitations of histologic methods. It can, however, be more or less achieved in instances of so-called specific diseases. From the knowledge at one's disposal today it must be concluded that rheumatic myocarditis is such a specific disease, the Aschoff body being the characteristic granuloma. Structures which do not conform to the classic description should not be definitely classed as Aschoff bodies, though they may resemble these. It is fully realized that the observer may fail to recognize some rheumatic lesions (Aschoff bodies) and thus fail to make the diagnosis of rheumatic myocarditis if he uses such rigid criteria for identification. On the other hand, he will be less likely to err than if

he considers cellular infiltrations resembling Aschoff bodies as true Aschoff bodies. In using strict criteria it must be concluded that up to this time typical Aschoff bodies have not been produced experimentally. This is true particularly for the researches of Klinge and Fricke, those of Moon and Stewart, Clawson (1928 b), Lowe and Lenke and others. It seems significant that no less an authority than Aschoff himself in a discussion on this subject in 1925 stressed that some of the lesions in question are beautiful examples of hyperergic inflammation but are not typical of Aschoff bodies, and again, four years later, warned against considering the histologic changes found in instances of anaphylactic shock analogous to the nodules seen in rheumatic fever.

In regard to a possible occurrence of rheumatic myocarditis not necessarily characterized by the presence of Aschoff bodies, Skworzoff expressed the opinion that in acute rheumatic fever an exudative inflammation occurs not only in serous cavities but also within the myocardium. In the myocardium such exudative inflammation is characterized by foci of inflammatory edema and the presence of cellular elements consisting particularly of lymphocytes and histiocytes, and also of neutrophilic leukocytes. Minute foci of necrosis are also sometimes encountered. It was stressed that these exudative changes may be seen in the vicinity of rheumatic nodules or may occur independent of these nodules. It was further pointed out that the clinical picture of rheumatic myocarditis is not the result of the presence of Aschoff bodies but is caused by this exudative inflammation of the myocardium. This type of myocarditis is seen most commonly in children.

In this respect it should also be mentioned that the few reports of the presence of Aschoff bodies in the hearts of patients who died of diseases other than rheumatic fever are used as further evidence against the specificity of the Aschoff body (Siegmund; Clawson (1929); Müller). It still remains to be proved, however, whether these lesions are Aschoff bodies (see Schmorl), and if they are, whether the patients had not had a previous rheumatic infection and whether the Aschoff nodules were anatomic evidence of past rheumatic myocarditis. A similar criticism was made some time ago by Fahr. Aschoff recently (1939) stated that in a thorough examination of hearts from patients who died of scarlet fever he was not able to find Aschoff bodies. According to Ravenna (1934), the occasional and even relatively frequent finding of Aschoff bodies in the hearts of patients with scarlet fever does not necessarily mean that these nodules are not specific for rheumatic fever. In this respect he emphasized the frequent occurrence of post-scarlatinal rheumatic fever. He also remarked (1937) that the geographic distribution of scarlet fever and rheumatic fever is about the same (Coburn and Pauli) and that these diseases often occur in the same

subjects. Hill noted that 121 of 600 rheumatic children had previously suffered from scarlet fever; both diseases begin with a sore throat. Rosenblum and Rosenblum stated that scarlet fever preceded the onset of rheumatic fever in 10 per cent of their patients. If it is admitted, as Schlesinger and co-workers and Ravenna (1939) suggested, that the streptococcic sore throat depresses the resistance against the rheumatic infection, which, according to these authors, is caused by a virus, the relation of scarlet fever and rheumatic fever might be better understood. Thus, the occurrence of Aschoff nodules in some of the patients with scarlet fever might be interpreted simply as the sign of a true, though in some instances latent, rheumatic infection.

There are many experimental studies on record relative to the production of Aschoff bodies, some of which were referred to before; others were summarized by Ravenna (1939). Here are mentioned only Rinehart and Mettier, who had studied the effect of scurvy and of scurvy combined with infection (beta streptococcus) on the heart valve and myocardium in the guinea pig. Lesions were found in the heart valves which in principle and character were thought to be fundamentally similar to the Aschoff reaction. They stated that, judging by the most severe standards, one could not, perhaps, fairly say that the Aschoff body had been produced in the heart muscle. However, proliferative lesions had been observed in the myocardium and beneath the mural endocardium in animals subjected to a combination of scurvy and infection which bore a strong resemblance to, and were believed to be fundamentally similar to, the reactions observed in rheumatic fever. These reactions were clearly different from the accumulations of lymphocytes with or without large mononuclear cells and foci of more or less mature fibroblasts occasionally encountered in control animals. To support the possibility that the lesions described in the myocardium resembled Aschoff bodies, they stated that it was well to remember that many authors had noted that the Aschoff body does not have a static structure but goes through an evolutionary cycle and that a considerable factor of time is probably necessary for the development of the lesion in its most characteristic form.

Chronic Infectious Arthritis.—Baggenstoss and Rosenberg studied cardiac lesions in this connection. The myocardial lesions in 8 instances were described as consisting of acute focal or diffuse myocarditis. Chronic active rheumatic myocarditis was also encountered. In 2 instances typical Aschoff bodies were seen in addition to focal accumulations of polymorphonuclear leukocytes, and in some regions small abscesses were encountered. In 2 cases evidence of healed rheumatic endocarditis was inferred from the presence of perivascular "onion skin" scars. These authors also stressed, quite emphatically, that rheumatic heart disease

can often be diagnosed accurately in the absence of typical Aschoff bodies if other characteristic changes are present. They stressed that in 10 of their cases the rheumatic nature of the lesions in question could not be seriously disputed.

Sydenham's Chorea.—Because of the supposed relationship between Sydenham's chorea and rheumatic fever, it seemed important to study reports of autopsies on patients who had this type of chorea in the absence of outspoken rheumatic fever. This was done for the special purpose of ascertaining whether or not anatomic changes similar to those seen in rheumatic fever also occur in Sydenham's chorea. Very few autopsy reports on patients with this type of chorea were found in the literature.

Fränkel stated that he found characteristic Aschoff nodules in the myocardium of a patient who died during an attack of Sydenham's chorea. The lesions were distributed diffusely throughout the septum. Likewise Huzella found typical Aschoff cells in the interstitial tissue in the myocardium of a 14 year old boy who died during chorea. There was also endocarditis, but no polyarthritis.

Schroeder cited the case of a 21 year old white woman who presented clinical evidence of acute endocarditis and pericarditis of uncertain origin. On the seventh day typical Sydenham's chorea developed, and three days later the patient died. The autopsy showed a number of small vegetations on the mitral valve, and the myocardium revealed typical Aschoff nodules.

Stevenson, quoted by Wilson, also observed a patient who died with severe Sydenham's chorea. The histologic examination of the myocardium disclosed Aschoff bodies.

Thalhimer and Rothschild reported the case of a 12 year old girl who two weeks before the onset of the terminal illness had had tonsillitis and complained of pain in the arms and legs. One week after the onset of the terminal illness, symptoms of Sydenham's chorea developed. The movements became extremely violent. The child died forty-eight hours later. The autopsy showed acute vegetative endocarditis of the mitral valve, and on histologic examination typical Aschoff bodies, present only in the adventitia of the arteries in the myocardium, were found.

These cases are interesting, but it seems that in not a single instance could rheumatic fever be ruled out as the cause of the myocardial changes. Whether Sydenham's chorea alone plays any role in the causation of the myocardial changes cannot be ascertained definitely but seems very unlikely.

Libman-Sacks Disease.—Perhaps closely related to rheumatic disease are the cardiac lesions found in patients presenting the Libman-Sacks

syndrome. Similar lesions have been described in lupus erythematosus. Libman and Sacks, in 1923, in their description of a form of valvular and mural endocarditis that had not been described to that time, stated that microscopically the endocarditic process had invaded the adjacent myocardium rather deeply, with destruction and replacement of many muscle fibers. There were foci of round cell infiltration and extreme fibrosis.

After an exhaustive study, Gross stated that changes in the myocardium were not severe. They consisted essentially of vascular alterations. The endothelial cells occasionally appeared high and cuboid. Proliferation, degeneration and "polyp formation" were sometimes observed. More characteristically, granular plugs were seen in the lumens of myocardial arterioles and venules, sometimes assuming a lobate form. The eccentric slitlike space representing what was left of the lumen was generally covered by endothelium continuous with the vascular endothelium proper. Occasionally, degenerated cells appeared intermingled with the granular material ("granular plugged vessels"). An apparently later stage of the same lesion showed partial organization of the plugs with the formation of two or more channels in the lumen by connective tissue septums ("channeled vessels"). Not infrequently, isolated vessels showed hematoxylin-stained bodies or multinucleated eosinophilic bodies. Occasionally these bodies appeared in the interstitial tissue. These various vascular lesions were observed with special frequency in the section through the posterior papillary muscle, but were found almost as often in the various portions of the ventricular and auricular myocardium.

Aside from these lesions there were foci of interstitial inflammation. These consisted of polymorphonuclear leukocytes, lymphocytes, macrophages and plasma cells. Purulent foci with occasional myocardial destruction and fibrosis were usually found in the cases in which terminal bacteremia had occurred. In the cases with previous rheumatic infection, lymphocytes and polymorphonuclear leukocytes generally predominated. These cases also showed characteristic interfascicular scars and occasionally vessels with intimal musculoelastic hyperplastic changes. In the uncomplicated cases of lupus erythematosus the predominating cells were usually plasma cells and peculiar large mononuclear cells. In addition, there were numerous histiocytes and fibroblasts. Such foci of plasma cells and mononuclear cells were occasionally associated with the thick, proliferating endothelial bud type of capillaries which have been described as occurring more frequently in the pericardium and valves. In the sections with extensive granular-plugged vessels there were usually minute infarcts in various stages of healing. No Aschoff body was present in any case.

Among the 240 cases of myocarditis which formed the basis for my own studies there were 30 instances of definite rheumatic myocarditis, characterized by the presence of outspoken Aschoff bodies as defined in an earlier paragraph. There were also 24 additional cases of myocarditis in which the inflammatory cells were partly confined to perivascular locations. Often these perivascular infiltrations resembled Aschoff bodies. Thus, these 24 instances may be classified as instances of a rheumatic type of myocarditis—particularly because of the accompanying endocardial lesions—but a definite diagnosis of "rheumatic myocarditis" could not be made. There were also 44 instances of subacute bacterial endocarditis, in many of which Aschoff bodies were present in the myocardium. However, these were not included among the instances of pure, uncomplicated rheumatic myocarditis.

(To Be Concluded)

Book Reviews

Essentials of Endocrinology. Arthur Grollman, Ph.D., M.D., associate professor of pharmacology and experimental therapeutics in the Johns Hopkins University. Pp. 480, with 74 illustrations. Price $6. Philadelphia: J. B. Lippincott Company, 1941.

This book aims to meet the needs of "the average medical reader" for a review of the present state of established knowledge in the field of endocrinology, clinical as well as experimental. The first chapter gives a basic survey of endocrinology, its scope, its history, its methods, including the origin, nature and clinical use of the hormones. Then come chapters on the various endocrine organs: the hypophysis and the pineal body; the thyroid, the parathyroids and the thymus; the islets of the pancreas and the adrenals; the male and female reproductive systems, with a chapter on the chemistry of the steroid hormones. Lastly, there is brief mention of hormones and presumptive hormones from nonendocrine sources. The present knowledge of the anatomy, the physiology, the hormones, the diseases and the clinical relations of the endocrine organs is reviewed thoroughly and objectively. The author has achieved admirably the objective set forth in his preface:

"Clinical endocrinology is frequently befuddled by accepting unproved assumptions as basic facts and building upon the insecure foundations thus established a maze of fanciful and ill-founded conjectures. When reduced to its experimentally established facts, clinical endocrinology can be placed on a scientifically sound basis. Since so much of endocrinology is based on observations in human disease, it is impossible to dissociate experimental from clinical endocrinology. I have, therefore, tried to correlate and cover both aspects of the subject in as complete a manner as is possible in a single volume."

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